Evidence Synthesis
Number 39

Screening for Human Immunodeficiency Virus in Pregnant Women: Evidence Synthesis

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0024
Task Order No. 2
Technical Support of the U.S. Preventive Services Task Force

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July 2005

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) and Evidence Syntheses through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, the Oregon Evidence-based Practice Center systematically reviews the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs and Evidence Syntheses—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER and Evidence Synthesis.

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We welcome written comments on this Evidence Synthesis. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850, or e-mail uspstf@ahrq.gov.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the current USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

Acknowledgments

This Evidence Synthesis was funded by the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force (USPSTF), and the investigators acknowledge the contributions of Gurvaneet Randhawa, MD, MPH, Task Order Officer, AHRQ, and David Lanier, MD, Medical Officer, AHRQ. Members of the USPSTF who served as leads for this project include: Janet Allen, PhD, RN, CS, FAAN; Ned Calonge, MD, MPH; Albert Siu, MD, MSPH; Diana Petitti, MD, MPH; and Mark Johnson, MD, MPH. The investigators thank Mark Helfand, MD, MS, for serving as a consultant; expert reviewers listed in Appendix F of this report for commenting on draft versions; Andrew Hamilton, MLS, MS, for conducting the literature searches; Rongwei Fu, PhD, for performing the statistical analyses; and Kim Villemyer and Christina Bougatsos for assisting with the manuscript.

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Structured Abstract

Context: An estimated 6,000 to 7,000 HIV-infected women give birth each year in the United States. Although the number of cases of perinatally acquired HIV infection has declined sharply in the U.S. since the early 1990's, an estimated 280-370 HIV-infected infants were born each year between 1999 and 2001.

Objective: To synthesize the evidence on risks and benefits of screening for HIV infection in pregnant women.

Data Sources: MEDLINE® (through June 30, 2004), Cochrane Clinical Trials Registry (2004, Issue 2), reference lists, and experts.

Study Selection: Controlled studies of screening and antiretrovirals, elective cesarean section, avoidance of breastfeeding, counseling, prophylaxis for opportunistic infections, immunizations, and routine monitoring and follow-up; observational studies of counseling, risk factors, accuracy of antibody testing, work-up, acceptability of screening and uptake of interventions, harms of interventions and screening, and long-term outcomes.

Data Extraction: Using preset criteria, the authors assessed the quality of included studies and abstracted information about settings, patients, interventions, and outcomes.

Data Synthesis: There are no published trials directly linking screening for HIV in pregnant women with clinical outcomes. In developed countries, the rate of mother-to-child transmission from untreated HIV-infected women ranges from 14% to 25%. Targeted screening of pregnant women with risk factor assessment would miss a significant proportion of infected persons. Standard office-based testing is highly (>99%) sensitive and specific, and initial studies of rapid HIV tests in labor and delivery settings found similar diagnostic accuracy. Rapid testing may facilitate timely interventions in those testing positive. HIV testing rates during pregnancy continue to vary widely in the U.S. and appear to be higher in states using 'opt-out' testing policies. Recommended interventions (combination antiretrovirals, elective cesarean section in selected patients, and avoidance of breastfeeding) are associated with transmission rates of 1%-2% in clinical trials and large observational studies. Shorter regimens are less effective, but also decrease the rate of transmission. Currently recommended combination antiretroviral regimens appear safe, but long-term follow-up is not yet available. Elective cesarean section is associated with an increased risk of mostly short-term adverse events. There are insufficient data to estimate the effects of interventions during pregnancy on long-term maternal outcomes.

Conclusions: Identification and treatment of asymptomatic HIV infection in pregnant women can result in major reductions in mother-to-child transmission rates. The estimated benefits from combination antiretrovirals appear to greatly outweigh the risk of short-term complications. In settings with a maternal prevalence of 0.15%, the estimated number needed to screen to prevent one case of maternal-to-child transmission using conservative estimates of intervention effectiveness ranged from 3,500 to 12,170, and in settings with a maternal prevalence of 5%, ranged from 105 to 365. Data are insufficient to accurately estimate the long-term benefits of

screening on maternal disease progression or other clinical outcomes (such as horizontal transmission).

Keywords: HIV, HIV infections, HIV seropositivity, mass screening, pregnancy

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Chapter 1. Introduction

This evidence synthesis focuses on screening for unsuspected human immunodeficiency virus (HIV) using HIV antibody (Ab) tests in pregnant women, including adolescents. The review will be used by the U.S. Preventive Services Task Force (USPSTF) to make recommendations regarding screening in pregnant women.

Since the USPSTF last published recommendations regarding HIV screening of pregnant women in 1996, there have been substantial changes in the management of pregnant women with HIV and in the rates of mother-to-child transmission. Although this report reviews the overall body of evidence regarding screening for HIV infection in pregnant women, it focuses on more recent data regarding the efficacy of combination antiretroviral regimens in prevention of mother-to-child transmission, harms associated with receipt of antiretrovirals in pregnancy, and the accuracy and acceptability of rapid testing.

Burden of Condition / Epidemiology

Women are the fastest growing group of persons with new HIV diagnoses, with 30% of new HIV infections diagnosed in women in 2001, and the incidence rising most rapidly among young minority women.[1, 2] There are 120,000-160,000 HIV-infected women (80% of childbearing age) residing in the U.S.[3] HIV seroprevalence among all U.S. women of childbearing age is estimated at 1.5 to 1.7 per 1000 women, but is higher in certain geographic areas.[4-6] Among women in New York City, for example, the prevalence of HIV among childbearing women was estimated at 0.62% in 2000.[7] As of 2003, approximately 3,788 perinatally infected persons were living with AIDS in the U.S., and there had been an estimated 4,961 cumulative deaths of children from perinatally acquired AIDS.[8] An estimated 6,000-7,000 HIV-positive women give birth each year in the U.S.[5] The number of cases of perinatally transmitted HIV, however, has declined sharply in the U.S. since the early 1990's.[5, 9] In 1994, for example, 213 cases of perinatally transmitted HIV were reported to the Centers for Disease Control and Prevention (CDC) by 25 states with confidential name-based reporting, compared to 26 cases in 2002.[10] The CDC estimates that 280-370 HIV-infected infants were born in the United States each year between 1999 and 2001.[11] In 2000, 40% of HIV-infected infants were born to mothers not known to have HIV infection before delivery.[12]

Healthcare Interventions

There is no effective vaccine to prevent HIV infection and no cure for chronic infection. In HIV-infected pregnant women, a major goal of interventions is to reduce the risk of mother-to-child transmission. Other important goals are to improve clinical outcomes in the mother, facilitate early identification of infected newborns, allow women to make informed future

reproductive choices, and prevent horizontal transmission through counseling on risky behaviors. Interventions for HIV-infected pregnant women include antiretroviral therapy, avoidance of breastfeeding, specific labor and delivery management techniques such as cesarean section before labor and before rupture of membranes (elective cesarean section), prophylaxis for opportunistic infections, immunizations, counseling to reduce high-risk behaviors, and regular monitoring and follow-up. In the U.S., receipt of combination antiretrovirals in conjunction with elective cesarean section in selected women and avoidance of breastfeeding is the standard of care to reduce mother-to-child transmission of HIV.[13, 14]

Management of HIV infection in pregnancy is a rapidly evolving area. Detailed and regularly updated U.S. guidelines regarding specifically recommended antiretroviral regimens in pregnancy,[14] chemoprophylaxis for opportunistic infections and immunizations,[15, 16] counseling methods,[17, 18] and labor management techniques[14, 19] are available. Guidelines recommending avoidance of breastfeeding by HIV-infected women remain unchanged.[18, 20] Current guidelines regarding the specific choice of initial antiretroviral therapy are based on a combination of results from clinical trials and observational studies, and special considerations such as convenience, potential risk to the fetus, side effect profile, and potential for drug interactions and the development of resistance.[14, 21]

Natural History

Mother-to-child transmission of HIV infection can occur during pregnancy (antepartum), during labor and delivery (intrapartum), and following delivery (postnatal). In the absence of breastfeeding, intrauterine transmission is thought to account for 25% to 40% of vertically infected infants, with the remainder infected during labor and delivery.[18] A high proportion of intrauterine transmission is thought to occur shortly before delivery.[22] Following delivery, HIV virus is present in and transmitted through breast milk.[23] Breastfeeding is thought to be the only important mode for postnatal transmission.[11, 24] In resource-poor settings in which women breastfeed for prolonged periods, postnatal transmission accounts for about 44% of infant cases.[25] A recent large (N=4,085) meta-analysis[26] of individual patient data from clinical trials in resource-poor settings found that the risk of late (after 4 weeks) postnatal transmission through breastfeeding was relatively constant at 8.9 transmissions/100 child-years of breastfeeding and higher than reported in a previous meta-analyses of observational studies,[27, 28] though definitions of late transmission varied.

Risk factors for peripartum transmission include high viral load,[29-37] immunologically or clinically advanced disease in the mother,[29, 38, 39], prolonged rupture of membranes,[30, 34, 37, 38, 40-43] maternal infection with other sexually transmitted diseases,[44] and procedures or events (such as abruptio placentae, fetal scalp electrode use, episiotomy, and second-degree or greater perineal laceration) associated with an increased probability of bodily fluid contact between mother and infant.[31, 44, 45] Illicit drug abuse was associated with an increased risk of maternal-to-child HIV transmission in most[30, 34, 37, 38, 40-42, 46] but not all[30, 36, 38, 47, 48] studies. Smoking,[30, 34, 41, 43] co-infection with hepatitis C, [34, 40] increased number of sexual partners or frequency of unprotected intercourse,[46] and the presence of maternal antiretroviral resistance mutations[49, 50] have also been associated with an increased risk of mother-to-child transmission.

Risk factors for clinical progression (in particular high viral load and low CD4 count) appear to be similar for HIV-infected pregnant and non-pregnant women. In developed countries, pregnancy does not appear to be an important independent predictor of clinical progression in chronically infected HIV-positive women.[51, 52] The clinical implications of significant viral load increases that have been observed following delivery in women who either received or did not receive antiretroviral therapy are unclear.[53-55]

Prior Recommendations

The USPSTF published guidelines for HIV screening in 1996.[56] At that time, the USPSTF recommended that clinicians should screen all high-risk pregnant women, including all women who live in states, counties, or cities with increased prevalence of HIV ("A" recommendation). Increased prevalence of HIV was defined as a seroprevalence in newborns of greater than or equal to 0.1%. The USPSTF found insufficient evidence to recommend for or against universal screening in low-risk pregnant women in low-prevalence areas.

The American Academy of Pediatrics and theAmerican College of Obstetricians and Gynecologists,[57] the Institute of Medicine,[58] and the Centers for Disease Control and Prevention[18] recommend universal counseling and voluntary testing for HIV in all pregnant women as part of routine prenatal care (Table 1).

Scope of Evidence Synthesis

The analytic framework in Figure 1 indicates the strategy we used to evaluate screening for HIV-1 infection in pregnant women. The key questions (Figure 2), which guided our literature review, were developed in conjunction with liaisons from the USPSTF and external expert reviewers.

The analytic framework shows the target populations, interventions, and intermediate and health outcome measures we examined. We included all pregnant women regardless of age. Our review considered the standard screening strategy for HIV-1 infection an office-based venipuncture with a repeatedly reactive serum anti-HIV enzyme-linked immunosorbent assay (EIA), followed by confirmatory Western blot or immunofluorescent assay for positive tests. The other major screening method that we considered was the use of rapid testing in women with unknown HIV status presenting to labor and delivery units. We also considered data on the use of home-based collection methods and tests using non-invasive samples such as saliva or urine in pregnant women. Viral load and CD4+ cell count testing was considered the standard work-up to determine the stage of infection in seropositive patients.

For treatment of HIV infection in pregnant women, we evaluated recommended antiretroviral therapies, prophylaxis for opportunistic infection, immunizations, avoidance of breastfeeding, labor management techniques such as elective cesarean section in women with viral loads >1,000 copies/ml, counseling to reduce risky behaviors, and routine monitoring and follow-up. We did not include interventions not shown to be effective or not recommended in current guidelines for antiretroviral-naïve pregnant women in the U.S., such as hydroxyurea,[14] HIV immune

globulin,[59] vitamin supplementation,[60] routine resistance testing,[61] and specific antiretroviral agents (such as efavirenz in the first trimester or the oral liquid formulation of amprenavir) or combinations (such as stavudine plus didanosine)[14, 21] that are no longer recommended. The major clinical outcome of interest in this review was mother-to-child transmission of HIV. We also reviewed data regarding the risk of clinical progression and mortality in HIV-positive women identified during pregnancy. Adverse outcomes of interventions in both mothers and infants were reviewed, emphasizing severe or intolerable events. We were also particularly interested in evidence regarding long-term maternal and child risks from antiretroviral therapy from exposure during pregnancy. Although antiretroviral therapy is associated with significant short-term side effects, many patients can be switched to effective alternative regimens, and intolerable or serious side effects are incorporated into intention-to-treat analyses of clinical outcomes.[62] Intermediate outcomes were loss of detectable viremia, improvement in CD4 counts, and changes in risky behaviors. We also reviewed harms from screening, work-up and treatment. Although the potential for the development of antiretroviral resistance is an important consideration in deciding which antiretroviral regimen to use during pregnancy, we primarily focused on reviewing the effects of resistance on long-term clinical outcomes.[63-66]

Chapter 2. Methods

Literature Search and Strategy

We searched the topic of HIV in the MEDLINE® and Cochrane Library databases. Most searches were carried out from 1983 (the year that HIV was characterized) through June 30, 2004. For searches on antiretroviral therapy, electronic searches were performed from 1998, the year that highly active antiretroviral therapy (HAART) was first recommended in U.S. guidelines,[67] and supplemented by an electronic search for systematic reviews of antiretroviral therapies from 1983. We performed a total of 13 searches covering the areas of risk factor assessment, screening tests, work-up, and interventions. Because a preliminary search found that search strategies limited by terms for pregnancy excluded relevant studies, we performed general searches on topics of interest and performed supplemental searches specifically related to pregnancy. Detailed electronic search strategies and results are presented in Appendix A. Periodic hand searching of relevant medical journals, reviews of reference lists, and peer review suggestions supplemented the electronic searches. Abstracts were not included in systematic searches, but major abstracts cited in reference lists or presented at recent conferences were included. Reviews, policy statements, and other papers with contextual value were also obtained.

Inclusion / Exclusion Criteria

A single reader reviewed all English abstracts. Papers were selected for full review if they were about HIV infection in pregnant women, relevant to key questions, and met inclusion criteria. For all key questions, articles were limited to those that evaluated the general population of pregnant women with HIV infection. Although the population of interest was pregnant women with unsuspected HIV infection who would be identified by screening, we included studies of pregnant women with a broad spectrum of chronic HIV disease in order to get a picture of the benefits and adverse effects of screening and treatment in patients with different degrees of immune deficiency. We included studies performed in the U.S., Australia, Canada, and Western Europe in which the epidemiology and management of chronic HIV infection are similar. When important studies for a specific key question had only been performed in other countries, these were included as well. Studies of non-human subjects and those without original data were excluded. Foreign language papers were considered if they were clinical trials and an abstract was available in English. We searched for relevant systematic reviews for all key questions. Additional key question-specific inclusion criteria are listed in Appendix B.

Data Extraction and Synthesis

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials and observational studies, which we rated as "good," fair," or "poor." We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPSTF and is described in detail elsewhere and summarized in Appendix C.[68] For included trials and systematic reviews, we abstracted information about setting, patients, interventions, and outcomes. We presented full evidence tables for selected high-priority key questions, and more concise tables for other key questions. We rated the overall body of evidence for each key question using the system developed by the USPSTF.

Size of Literature Reviewed

Investigators reviewed 5,993 abstracts identified by the searches (Appendix D). From the searches, 1,866 full-text articles were reviewed. An additional 809 non-duplicate articles identified from reference lists and experts were also reviewed.

Chapter 3. Results

Key Question 1. Does Screening for HIV in Asymptomatic Pregnant Women Reduce Mother-to-Child Transmission or Premature Death and Disability?

We identified no randomized trials or observational studies comparing clinical outcomes from screening or not screening pregnant patients in the general population. Although the number of infants with perinatally acquired HIV transmission has markedly declined in the U.S., this is probably due to a combination of increased screening during pregnancy and increased development and acceptance of interventions to prevent transmission, and some HIV-positive women may have been identified before their pregnancy.[5, 18] We identified no studies estimating the relative impact of these factors on transmission rates.

Key Question 2. Can Clinical or Demographic Characteristics (Including Persons in Specific Settings) Identify Subgroups of Asymptomatic Pregnant Women at Increased Risk for HIV Infection Compared to the General Population of Pregnant Women?

Risk factors for HIV infection appear to be similar in pregnant and non-pregnant women and are largely unchanged since 1996. The 1996 USPSTF recommendations defined persons at increased risk of HIV infection as those seeking treatment for sexually transmitted diseases; past or present injection drug users; persons who exchange sex for money or drugs and their sex partners; women whose past or present sex partners were HIV-infected, bisexual, or injection drug users; and persons with a history of transfusion between 1978 and 1985.[56] Current CDC guidelines also consider unprotected vaginal or anal intercourse with more than one sex partner a high-risk behavior.[17] Late or no prenatal care has also been associated with a higher risk for HIV infection.[69]

A large study of 73,472 women tested at U.S. federally funded prenatal or obstetrics clinics found that 0.6% were positive for HIV.[70] Smaller studies of pregnant women reported prevalence rates ranging from 0.13% to 5%.[7, 71, 72] In the U.S., there are regional variations in the prevalence of HIV infection, and HIV-positive women are more likely to be African-American or Hispanic.[10] Heterosexual transmission has replaced intravenous drug abuse as the most common route of HIV infection among American women. In 30 U.S. areas with confidential name-based reporting, for example, 79% (5,949 of 7,503) women diagnosed with HIV or AIDS in 2002 identified heterosexual contact as their risk factor.[10] More than 25% of U.S. women with AIDS reside in smaller cities and rural areas.[73]

Targeted screening of HIV-positive pregnant women based on the presence of risk factors may miss a substantial proportion of infected persons.[74] Not screening HIV-infected women unaware of their status due to lack of reported risk factors could result in missed opportunities for perinatal HIV prevention and other interventions. Observational studies in high- and low-prevalence settings (all published prior to 1996) found that between 8%[75] and 57%[76] of HIV-infected pregnant women reported identifiable risk factors.[77-81] Changes in the criteria used to define high-risk behaviors and varying stringency of risk factor assessment, however, complicate interpretation of these results. In two studies, for example, the number of sexual partners was not determined, even though current CDC guidelines consider unprotected intercourse with more than one sexual partner a high-risk behavior.[75, 79] In another study, more detailed risk assessment following testing identified substantially more high-risk behaviors than pre-test risk assessment.[77]

Prior to 1995, HIV screening was routinely recommended by less than 50% of U.S. physicians.[82] After zidovudine was shown to be effective in reducing vertical transmission,[83] universal prenatal counseling and voluntary HIV testing was recommended in 1995 by the U.S. Public Health Service[20] and the American Academy of Pediatrics,[73] and appeared to contribute to an increase in the number of HIV diagnoses in pregnant women in the U.S.[84] In a seven-state surveillance study, for example, the proportion of HIV-infected women diagnosed before delivery increased from 70% to 80% between 1993 and 1996.[85] In one British study, the incidence of known HIV seropositivity at delivery nearly doubled (0.26% to 0.48%) after the implementation of a universal voluntary screening program.[75] In another British study, however, over 50% of cases identified by anonymous testing were not detected after a universal counseling and voluntary testing policy was implemented, despite increased uptake rates.[86] We identified no U.S. studies since 1995 evaluating the effectiveness of targeted compared to universal counseling and screening. A recent survey of 138 physicians in Alabama who provide prenatal care found that 12% reported that they did not offer universal prenatal HIV counseling and testing despite guidelines.[87]

Key Question 3. What Are the Test Characteristics of HIV Antibody Test Strategies in Pregnant Women?

The use of repeatedly reactive enzyme-linked immunosorbent assay (EIA) followed by confirmatory Western blot (WB) or immunofluorescent assay (IFA) on an office-based venipuncture specimen remains the standard strategy for diagnosing HIV-1 infection, and is associated with a sensitivity and specificity greater than 99%.[88, 89] The diagnostic accuracy of standard HIV testing is thought to be similar for pregnant and non-pregnant persons, though indeterminate results may occur slightly more frequently among parous and pregnant women.[90]

Rapid HIV antibody tests provide results in 5-40 minutes, compared to one to two weeks for standard testing.[6] Such testing provides an opportunity to reduce transmission of HIV from pregnant women who received no prenatal care or who were not tested earlier in pregnancy for other reasons. Such point of care testing in labor may also allow providers to avoid obstetric practices that may increase the risk of transmission, and gives providers the opportunity to counsel the mother against breastfeeding.[6, 18] Notification of rapid test results prior to the availability of confirmatory results is recommended in situations in which preliminary test results

might benefit tested persons, such as in women with unknown HIV status presenting in active labor.[91] However, this could result in unnecessary exposure to antiretroviral or other therapies if the rapid test result is a false positive. Most studies measure the diagnostic accuracy of rapid tests before confirmatory testing, though CDC guidelines recommend routine confirmation of positive rapid tests.[92]

The Food and Drug Administration (FDA) has approved four rapid HIV tests (Uni-Gold™ Recombigen®, Reveal™ G2, OraQuick® Advance, and Single Use Diagnostic System [SUDS]), but one (SUDS) is not currently being manufactured. In studies of mostly non-pregnant persons, the sensitivities of rapid HIV tests currently available in the U.S. ranged from 96% to 100% and the specificities >99% compared to standard testing.[93-98] The OraQuick® test performed slightly better than the other rapid tests on blood samples and was calculated to have a positive predictive value near 100% even in low-prevalence settings.[6] Though a newer version of the OraQuick® test (OraQuick® ADVANCE Rapid HIV-1/2 Antibody Test) has recently been FDA approved for testing of oral as well as whole blood specimens, no studies of the diagnostic accuracy of rapid oral specimen testing are yet available.

We identified three good-[99-101] and four fair-quality[102-105] studies evaluating the diagnostic test characteristics of rapid HIV testing during pregnancy that used standard EIA and confirmatory Western blot as the reference standard (Table 2). Two of these were conducted among pregnant women in the U.S.,[99, 100] but only one[99] evaluated a rapid HIV test currently available in the U.S. This was a good-quality prospective study that evaluated the test characteristics of the OraQuick® Rapid HIV-1 serum test among 5,744 women presenting in labor in six U.S. cities between 2001 and 2003. Compared to standard testing, the sensitivity was 100% (95% CI, 90%-100%), specificity 99.9% (95% CI, 99.78%-99.98%), positive predictive value 90% (95% CI, 75%-97%), and negative predictive value 100%, with a prevalence of 0.59%. In studies of rapid tests not currently available in the U.S., sensitivity ranged from 95.8% to 100%, specificity ranged from 98% to 100%, and positive predictive values ranged from 33% to 100%.[100-105] One African study comparing a strategy of confirming one positive rapid test with a second, different rapid test found a sensitivity of 99.6% and specificity 99.9% compared to standard testing, but this strategy is not used in the U.S.[106]

We identified no studies evaluating the diagnostic accuracy of HIV tests in pregnant women based on home-based sampling kits, non-invasive (urine or oral) specimens, or testing of pooled samples with polymerase chain reaction to detect acute infection using standard testing as the reference standard. Although one Indian study found a lower sensitivity with the OraQuick® test on saliva compared to plasma (75.0% vs. 86.4%), it did not use standard EIA plus WB as the reference standard, and may have been related to decreased saliva due to hot local conditions.[107]

Repeat testing of women who screen HIV-negative during early pregnancy could identify those who are infected after initial testing but before delivery. Whether to repeatedly screen during pregnancy and the optimal timing of repeat testing would depend in part on the frequency of new HIV infections. The incidence of HIV infection among average-risk U.S. women has been estimated at 0.17 per 1,000 person-years,[2] and among a high-risk population of pregnant women at 6.2 per 1,000 person-years.[108] Using these rates, one model estimated that repeat testing in the third trimester after a negative test in the first trimester would detect 5.3 infections per 100,000 average-risk women tested and 192 infections per 100,000 high-risk women tested.[109]

Key Question 4. What Are the Harms (Including Labeling and Anxiety) Associated with Screening? Is Screening Acceptable to Pregnant Women?

False-positive diagnoses are rare with standard testing even in low-risk settings.[110] Most of the evidence regarding the frequency and harms from false-positive diagnoses in pregnant women is anecdotal, but could include elective pregnancy termination based on incorrect test results, anxiety, discrimination, or altered partner relationships.[111] In a recent U.S. study of rapid HIV testing in women with undetermined status presenting in labor, 4 out of 4,849 tested women had a false-positive test and briefly received antiretroviral prophylaxis prior to receiving results of confirmatory testing.[99]

False-negative tests during pregnancy may occur in recently infected individuals or those with advanced disease, and could give false assurance. False-negative and true-negative tests could encourage continued risky behaviors unless patients are appropriately counseled, but we identified no studies evaluating changes in behaviors in pregnant women after negative HIV tests. Indeterminate test results are likely to cause anxiety while additional testing is performed, but data are limited on rates and consequences of indeterminate tests in pregnant women.[112]

True-positive tests can result in anxiety, depression, social stigmatization, changes in relationships with sexual partners, and discrimination.[73, 74] Most studies on these harms have been performed in non-pregnant populations. One small (N=40) study of U.S. women found that mean anxiety and depression scores were significantly ($p<0.05$) higher for HIV-positive women compared to matched uninfected controls.[113] A potential increase in the risk of intimate partner violence for pregnant women after disclosure of HIV status is especially concerning. A recent good-quality cohort study, however, found that the rate of violence during pregnancy was similar between HIV-infected women and seronegative at-risk pregnant women, and that receiving an HIV diagnosis prenatally did not increase risk.[114] Disclosure-related violence occurred, but was rare. There are insufficient data to determine whether diagnosis of HIV during pregnancy is associated with an increased risk of suicide.[115] One small study found a nonsignificant trend towards increased partner dissolution in HIV-positive pregnant women compared to matched seronegative controls.[113]

There remains general consensus that HIV testing should be voluntary and performed after obtaining informed consent.[17] Mandatory testing of pregnant women has been debated, but might result in women avoiding prenatal care to avoid testing.[116] Uptake of voluntary HIV testing has increased since recommendations regarding universal counseling were issued. A large U.S. telephone survey, for example, found that testing rates in pregnant women had increased from 41% in 1995 to 60% in 1998.[117]

A good-quality systematic review found that acceptance rates for voluntary HIV antibody testing among more than 174,000 pregnant women in 25 studies published through 1995 ranged from 23% to 100%.[118] Recent data from 16 U.S. states and 5 Canadian provinces found a similar range of prenatal HIV testing (25% to 98%) among pregnant women.[119] Smaller recent U.S. studies reported testing rates that also fell within those ranges.[120, 121]

Several patient or provider factors appear to affect testing rates. One randomized trial found that antenatal uptake rates were significantly higher in patients offered HIV testing (35%) than in patients for whom the test was available, but did not receive a direct offer (6%).[122] Strong

provider endorsement of testing appears to be a predictor of HIV testing acceptance.[121, 123] Lack of prenatal care, on the other hand, was a predictor of declining to be tested in a large observational study.[124] Other factors associated with increased acceptance of voluntary HIV testing were inconsistent across studies and included specific ethnic or racial groups, age groups, educational level, marital status, and socioeconomic status.[120, 121, 125, 126]

Policy factors also appear to influence testing rates. For example, some jurisdictions have adopted an 'opt-out' (pregnant women are informed that an HIV test is being conducted as a standard part of prenatal care and that they may refuse it) compared to an 'opt-in' (pregnant women are required to consent specifically to an HIV test) policy. Testing rates appeared to be higher in states and Canadian provinces that used an 'opt-out' policy (71% to 98% vs. 25% to 83% with opt-in testing).[119] Other studies from the U.S. and Canada have also reported high (85% to 88%) rates of testing acceptance using an opt-out approach.[122, 127, 128] The implementation of a mandatory newborn testing policy with expedited results was associated with increased prenatal testing rates in two states.[119] We identified no studies specifically evaluating the effect of name-based reporting on rates of prenatal screening, though in a Canadian study in which an opt-out approach and name-based reporting were introduced near-simultaneously, testing rates increased.[128]

Newer screening methods such as home sample collection kits, rapid tests, on-site testing, and non-invasive sampling could increase rates of voluntary prenatal HIV testing.[6] The recent observational MIRIAD (Mother-Infant Rapid Intervention At Delivery) study of pregnant women (N=5,744) presenting to labor and delivery units with undocumented HIV status found that 84% accepted rapid testing.[99] Higher acceptance was associated with younger age, being Black or Hispanic, gestational age less than 32 weeks, and having no prenatal care. Lower acceptance was associated with being admitted between 4 pm and midnight, possibly because of fewer available hospital personnel.[99] We identified no studies evaluating the effect of alternative sampling methods (urine or saliva sampling, home-based collection) on the uptake of prenatal HIV testing.

Key Question 5. How Many HIV-Infected Pregnant Women Who Meet Criteria for Interventions Receive Them?

Current guidelines recommend that antiretroviral *prophylaxis* be offered to all HIV-infected pregnant women in order to reduce the risk of mother-to-child transmission.[14] Some women also meet criteria for antiretroviral *treatment* to improve maternal outcomes, which is determined by the CD4 count and viral load at the time of diagnosis. HAART is recommended for pregnant women according to the same guidelines used in the general population.[14] For pregnant women who do not meet guidelines for HAART, the decision to use other less-intense antiretroviral regimens must be balanced against their potential for inducing resistance.[129-131]

We identified one large U.S. cohort study (the Women and Infants Transmission Study) that reported maternal CD4 count and viral load in women enrolled during pregnancy since 1989.[34] It found that 13% (70/546) had CD4 counts <200 cells/mm^3 and 56% (307/546) had CD4 counts <500 cells/mm^3. Ten percent (57 of 551) had viral loads <1,000 copies/ml.

HIV-tested persons may not return for their test results or regular medical care. In the U.S., however, test notification rates among pregnant women appear high. In one large U.S. study, for

example, 91% (3,690 of 4,062) of tested pregnant women received their results.[132] In settings with low return rates, rapid testing could increase notification rates by providing patients with same-visit results. We identified one African randomized trial that found that rapid HIV testing increased rates of notification of results compared to standard testing (96% versus 65%) among pregnant HIV-positive women not presenting during labor.[133]

HIV-infected women appear to widely accept and receive antiretroviral drugs during pregnancy. Several recent U.S. studies found that antiretroviral drugs were used by HIV-infected women in more than 90% of pregnancies, with a recent trend towards increased combination (HAART and non-HAART) regimens (58% to 80% in 1998-1999).[37, 134-137] In the Woman and Infants Transmission Study, approximately 60% of enrolled pregnant women received HAART in 1999.[37] An earlier multi-state observational study found that the proportion of HIV-infected women who received prenatal zidovudine increased from 27% to 83% between 1993 and 1996.[85] In a recent U.S. observational study, all (n=18) HIV-infected pregnant women diagnosed during labor in time to receive intrapartum zidovudine received it.[99] Elective cesarean section rates for HIV-infected pregnant women also are rising. In several recent large U.S. observational studies, scheduled cesarean section rates ranged from 37% to 50%.[134, 137, 138]

HIV-infected women who are not tested during pregnancy may not be identified until they present with symptomatic illness or immunologically advanced disease. We identified no studies, however, comparing the proportion of women diagnosed late among those who were tested versus those not tested during pregnancy. Studies in the general population of HIV-infected persons suggest that diagnosis at immunologically advanced stages of disease is associated with poorer response to antiretroviral therapy.[139-144]

Key Question 6. What Are the Harms Associated with the Work-up for HIV Infection in Pregnant Women?

We identified no studies estimating potential harms (anxiety, labeling, effects on close relationships, increased risky behaviors) from checking viral loads or CD4 counts in HIV-infected pregnant women.

Key Question 7a. How Effective Are Interventions (Antiretroviral Prophylaxis [to Prevent Mother-to-Child Transmission] or Treatment [to Improve Maternal Outcomes], Avoidance of Breastfeeding, Elective Cesarean Section [in Selected Patients] or Other Labor Management Practices, Counseling on Risky Behaviors, Immunizations, Routine Monitoring and Follow-up or Prophylaxis for Opportunistic Infections) in Reducing Transmission Rates or Improving Clinical Outcomes (Mortality, Functional Status, Quality of Life, Symptoms, or Opportunistic Infections) in Pregnant Women with HIV Infection?

Antiretroviral Drugs

Zidovudine alone has been shown to be efficacious and effective in reducing the risk of mother-to-child transmission of HIV. In the absence of antiretroviral prophylaxis, the risk for transmission of HIV from mother to infant is 14% to 25% in developed countries, and 13% to 42% in countries with high rates of breastfeeding.[145] The landmark Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 study found that a three-phase maternal and infant zidovudine regimen starting at 14 to 34 weeks gestation (median 26 weeks) through 6 weeks postpartum in non-breastfeeding women decreased the risk of mother-to-child transmission by nearly 70%, from about 25% to about 8%, compared to placebo.[83] We identified a good-quality systematic review of seven randomized controlled trials that found that any zidovudine treatment (including shorter courses and in breastfeeding women) significantly reduced the risk of mother-to-child transmission compared to placebo (OR 0.46, 95% CI 0.35-0.60), with no significant heterogeneity between trials.[146] Zidovudine was also associated with decreased risk of infant death within the first year of life (OR 0.57, 95% CI 0.38-0.85) and decreased risk of stillbirth (RR 0.31, 95% CI 0.11-0.90).

In the U.S., treatment of pregnant women infected with HIV has evolved from zidovudine alone to combination antiretroviral regimens.[147] We identified one trial of continuous full-course combination antiretrovirals (nelfinavir or nevirapine plus zidovudine) that was discontinued early (after 38 women enrolled) because of a high rate of treatment-limiting or serious side effects in the nevirapine arm.[148] Other randomized trials of full-course combination antiretrovirals in pregnant women are not available. We identified four large American or European cohort studies (three good-quality, one fair-quality) evaluating the relative effectiveness of two or more drug antiretroviral regimens versus placebo or full-course (PACTG 076 protocol) zidovudine monotherapy in non-breastfeeding women (Tables 3 and 4).[37, 48, 149, 150] In all four studies, regimens with more antiretroviral drugs were superior to regimens with fewer antiretroviral drugs for preventing mother-to-child transmission (Table 5). The only study that specifically evaluated the effectiveness of HAART regimens compared to no antiretrovirals reported an adjusted odds ratio of 0.13 (95% CI, 0.06 to 0.27) for prevention of mother-to-child transmission.[149] One study[48] calculated an adjusted odds ratio of 0.07 (95% CI 0.02 to 0.23) for

two or more drug antiretroviral regimens compared to no antiretrovirals, and two others[37, 150] reported adjusted odds ratios of 0.22 (95% CI 0.10 to 0.50) and 0.30 (95% CI 0.09 to 1.02) for two or more drug regimens compared to full-course (three-part PACTG 076 protocol) zidovudine monotherapy. One study evaluated the effectiveness of HAART versus zidovudine monotherapy (adjusted OR 0.27, 95% CI 0.08 to 0.94).[37] The proportion of women undergoing cesarean section in these studies ranged from 16% to 44%.

The addition of single-dose intrapartum (maternal) and postnatal (infant) nevirapine to antiretroviral regimens initiated before 34 weeks has been evaluated in two good-quality randomized controlled trials performed in non-breastfeeding settings (Tables 6 and 7).[151, 152] The first trial, from Thailand, found that the addition of single doses of intrapartum and postnatal nevirapine to a slightly abbreviated course of zidovudine monotherapy (from 28 weeks gestation to 1 week postnatal) reduced mother-to-child transmission from 6.3% to 1.9%.[152] An earlier international randomized clinical trial, on the other hand, found that the addition of single-dose intrapartum and postnatal nevirapine to primarily (77%) combination antiretroviral regimens did not further decrease already low transmission rates (1.4% to 1.6%).[151]

Shorter courses of antiretroviral prophylaxis have also been developed for use in resource-poor countries. Data from these studies may also help guide management of women in the U.S. who were not diagnosed early enough to receive a full course of antiretroviral prophylaxis. Several clinical trials have evaluated shorter courses of antiretrovirals in women diagnosed after 34 weeks, but before presenting in active labor (Tables 8, 9, and 10). A randomized controlled trial from Thailand (the Perinatal HIV Prevention Trial) found that the risk of transmission using a "short-short" course of zidovudine (from 35 weeks in pregnancy for the mother, intrapartum, and for the newborn until 3 days old) was higher (OR 2.33, 95% CI 1.16-4.68) than the risk using a "long-long" course (from 28 weeks in pregnancy, intrapartum, and for the infant until 6 weeks old).[153] However, intermediate courses were similar in efficacy to the full course. An earlier Thai randomized controlled trial found that prophylaxis with zidovudine from 36 weeks and intrapartum without neonatal treatment was associated with a transmission rate similar to that seen in the short-short leg of the Perinatal HIV Prevention Trial (9.4% vs. 10%), suggesting that short courses of neonatal zidovudine added little benefit.[154] Both trials were in non-breastfeeding women. Another recent good-quality randomized controlled trial in African breastfeeding women found that short-course zidovudine combined with lamivudine from 36 weeks gestation reduced mother-to-child transmission from 15.3% (in women receiving placebo) to 5.7 % (OR 0.37; 95% CI, 0.21-0.65).[155] Shorter courses of zidovudine and lamivudine were less effective. Two other trials of breastfeeding women in Africa found that zidovudine from 36 weeks reduced mother-to-child transmission of HIV from 26.1% to 27.5% in women in the placebo arms compared to 16.5% to 18.0% in the intervention arms.[156, 157]

Some HIV-infected pregnant women may not be diagnosed until very late in pregnancy or during labor. We identified four good-quality African randomized controlled trials of breastfeeding women evaluating the effects of very abbreviated regimens for this situation (Tables 8, 9, and 10).[158-162] Three of these trials evaluated regimens that consisted of antiretroviral prophylaxis administered during labor and postexposure treatment for the infant. One clinical trial found that in this setting, nevirapine was significantly better at reducing vertical transmission (11.8%) than zidovudine (20.0%).[160, 162] Another trial found that nevirapine administered during labor and to the infant was associated with a similar rate of vertical transmission (14.1%) compared to the same regimen with zidovudine also administered to the infant (16.3%).[161] In the third trial, short-course nevirapine was associated with a 12.3%

transmission rate compared to 9.3% with zidovudine plus lamivudine.[158] The fourth trial compared regimens of neonatal postexposure prophylaxis without maternal prophylaxis.[159] It found that prophylaxis of the newborn alone was associated with higher transmission rates (15.3% for nevirapine plus zidovudine versus 20.9% for nevirapine alone) than seen in clinical trials that included maternal prophylaxis.

A recent U.S. observational study of rapid testing for women with unknown HIV status presenting during labor and who received zidovudine prophylaxis with or without nevirapine found that the transmission rate was 9% (3 of 32).[99]

We identified no studies evaluating clinical outcomes (clinical progression, death, quality of life, or horizontal transmission) associated with different antiretroviral regimens for HIV-infected women identified during pregnancy. In one study of women who received zidovudine plus single-dose nevirapine intrapartum and subsequently started a nevirapine-based antiretroviral regimen, no harmful effects on clinical outcomes were observed after six months, but longer term follow-up is not yet available.[131]

Breastfeeding

We identified two meta-analyses of observational studies that found that breastfeeding was associated with an overall increased rate of mother-to-child transmission of HIV of 14% to 16% (Table 11).[24, 27] In two other meta-analyses, the cumulative rate of late transmission was 9.3% after 18 months in one meta-analysis of individual patient data from clinical trials that defined late transmission as occurring after four weeks,[26] and 9.2% after 18 months in an earlier meta-analysis of observational studies that defined late transmission as occurring after 2.5 months.[28] Factors associated with an increased risk of breastfeeding transmission include low maternal CD4 count, detectable virus in breast milk, higher serum viral load, acute HIV infection, nipple lesions, mastitis, oral candidiasis in the infant, longer duration of breastfeeding, younger maternal age, lower parity, and male sex of the infant.[23, 26, 163]

We identified no randomized controlled trials evaluating the rate of vertical transmission associated with breastfeeding in the U.S. or in women on antiretroviral therapy. We identified one large prospective Italian cohort study of 3,770 children that found that breastfeeding significantly increased transmission rates when adjusted for other factors including antiretroviral use (adjusted OR 10.20 [2.73-38.11]).[48] An African trial of formula versus breastfeeding among women not receiving antiretroviral therapy found that breastfeeding was associated with a probability of vertical transmission of 36.7% (95% CI, 29.4%-44.0%) at 24 months compared to 20.5% (95% CI, 14.0%-27.0%) in the formula feeding arm, and a mortality rate of 24.4% (95% CI, 18.2% to 30.7%) compared to 20.0% (95% CI, 14.4%-25.6%).[164] Another African observational study suggested that mixed feeding (both formula and breast) was associated with a higher risk of mother-to-child transmission of HIV than exclusive breastfeeding, though confidence intervals overlapped.[165]

Pregnancy and Labor Management

Labor management techniques that minimize contact between infected maternal bodily fluids and the fetus could decrease the risk of mother-to-child HIV transmission. Elective cesarean section has been the most extensively studied labor management technique.[35, 146, 166-172]

One good-quality European cohort study evaluated the effectiveness of elective cesarean section in the HAART era.[149] It found an odds ratio of 0.33 (95% CI 0.11 to 0.94) for mother-to-child transmission with elective cesarean delivery compared to vaginal delivery when adjusted for antiretroviral therapy, prematurity, and maternal CD4 count and viral load. In the subgroup of women receiving HAART, the odds ratio was 0.64 (95% CI 0.08 to 5.37) for elective cesarean compared to vaginal delivery, and in the subgroup with undetectable viremia, the odds ratio was 0.07 (95% CI 0.02 to 0.31) for elective cesarean compared to vaginal or emergency cesarean delivery.

Other studies evaluating the effectiveness of elective cesarean section were conducted prior to the widespread use of combination antiretroviral regimens. We identified one good-quality randomized clinical trial examining the impact of elective cesarean section on mother to child HIV transmission (Table 12).[171] This European study of 370 mother-child pairs found a reduction in vertical transmission from 10.5% in women randomized to vaginal delivery to 1.8% in those randomized to elective cesarean section (p=0.009). Among 119 babies delivered to women who received zidovudine and underwent cesarean section, the rate of HIV infection was 0.8%. We also identified a meta-analysis of individual patient data from 8,533 mother-child pairs in 15 prospective cohort studies that found a 50% reduction in the likelihood of vertical transmission with elective cesarean section compared to other modes of delivery (OR 0.43, 95% CI 0.33-0.56).[170] The benefits of elective cesarean section appeared additive with prophylactic zidovudine monotherapy, with the likelihood of transmission reduced by approximately 87% with both elective cesarean section and full-course zidovudine compared to other modes of delivery (non-elective cesarean section or vaginal delivery) and no antiretroviral therapy (adjusted OR 0.13, 95% CI 0.09-0.19). A meta-analysis of 7 European and U.S. prospective cohort studies of 1,202 women with viral loads <1,000 copies/ml also found that cesarean section (elective and non-elective) was independently associated with a lower risk for transmission (adjusted OR 0.30, p=0.22), but the overall transmission rate was low (3.6%) and reduced by antiretroviral therapy alone (primarily zidovudine) to about 1%.[173] We identified no studies evaluating the additive effects of elective cesarean section in women receiving multi-drug antiretroviral regimens.

We identified one good-quality systematic review that evaluated the risk of invasive procedures during pregnancy and found only one prospective cohort study that met inclusion criteria.[174] In that study, amniocentesis was associated with a significantly increased rate of mother-to-child transmission of HIV.[44] We also identified one good-quality systematic review that found no association between vaginal disinfection with chlorhexidine and reduced mother-to-child transmission of HIV (OR 0.93, 95% CI 0.63-1.38).[175]

Counseling on Risky Behaviors

We identified no studies estimating the effects of counseling HIV-infected pregnant women regarding risky behaviors on vertical or horizontal transmission rates.

Immunizations

We identified no clinical trials or observational studies estimating clinical benefits of recommended immunizations in HIV positive pregnant women.

Prophylaxis for Opportunistic Infections

We identified no clinical trials or observational studies estimating clinical benefits of recommended prophylaxis for different opportunistic infections in HIV infected pregnant women.

Routine Monitoring and Follow-up

HIV-infected women identified during pregnancy might benefit from appropriate monitoring of their status (such as following CD4 count and viral load) or regular follow-up to identify early signs of symptomatic illness, in addition to other interventions. We identified no studies estimating the clinical benefits of linking women with health care for routine monitoring after identification of HIV infection during pregnancy.

Key Question 7b. Does Immediate Antiretroviral Treatment in HIV-Infected Pregnant Women Result in Improvements in Clinical Outcomes Compared to Delayed Treatment until Symptomatic?

Some HIV-infected women who choose to use an antiretroviral regimen during the perinatal period to prevent vertical transmission may not receive long-term HAART in the postnatal period because of low viral loads, high CD4 counts, loss to follow-up, or other reasons. We identified no studies estimating the effects of delayed or discontinued versus continuous HAART in HIV-infected women identified during pregnancy.

Withholding antiretrovirals in the first trimester may be an option for women with low viral loads who have a lower risk of transmitting HIV and wish to minimize the risk for congenital anomalies or reduce the likelihood for poor adherence because of pregnancy-related nausea.[14] However, we identified no trials examining the effects of delaying antiretroviral prophylaxis or treatment until after the first trimester on mother-to-child transmission rates or other clinical outcomes.

Key Question 7c. How Well Do Interventions Reduce the Rate of Viremia, Improve CD4 Counts, and Reduce Risky Behaviors? How Does Identification of HIV Infection in Pregnant Women Affect Future Reproductive Choices?

In HIV-infected persons in general, HAART is more effective than less intense regimens in achieving sustained virological suppression and improved CD4 counts.[176] In pregnant women, HAART appears similarly effective for improving intermediate outcomes.[39]

We found little evidence on the effect of counseling HIV-positive pregnant women on subsequent changes in risky behaviors that may be associated with increased rates of vertical transmission, such as unprotected intercourse, cigarette smoking, and hard drug use. A small U.S. study found that 40% of 20 HIV-positive and 20% of 20 HIV-negative women reported always using condoms.[113] In another study, most HIV-positive women with a history of intravenous drug use who decreased needle sharing changed their behavior before learning their HIV status.[177]

Counseling HIV-infected women could also lead to behavior changes that might decrease the risk of horizontal transmission, but most studies evaluating the effects of counseling on behavior changes have been performed in non-pregnant persons. In two good-quality systematic reviews, there was mixed evidence regarding the effectiveness of counseling on changing behaviors among HIV-infected women.[178, 179] In one small U.S. study, a high proportion of both HIV-positive and HIV-negative pregnant women had unprotected intercourse after testing.[113]

Knowledge of HIV infection status could affect future reproductive choices, but we identified few studies evaluating the effects of identifying and counseling HIV-infected pregnant women on subsequent contraceptive choices or pregnancy, sterilization, and abortion rates.[180-182] In two studies, HIV seropositivity was associated with a lower rate of pregnancy[182] or trend towards lower rate[181] than in uninfected women, but another study found that the rate of pregnancy in HIV-infected women appears to be increasing.[183] One U.S. study found that 27% of HIV-infected women chose tubal ligation compared to 15% in uninfected controls, and oral contraceptive use was less likely in seropositive women.[181] Two other non-comparative U.S. studies reported rates of tubal ligation among HIV-infected women of 24% and 27%.[85, 180] An African study of single session postpartum counseling in HIV-infected women found that the intervention did not appear to influence decisions on condom use or reproductive behavior.[184] No differences in pregnancy termination rates between HIV-infected and uninfected women were seen in two U.S. studies.[113, 185]

Key Question 8. What Are the Harms (Including Adverse Effects from In Utero Exposure) Associated with Antiretroviral Intervention and Elective Cesarean Section?

Harms of Antiretrovirals to Mothers

Receipt of antiretrovirals during pregnancy is associated with significant short-term non-obstetric adverse events, but these often resolve after stopping the offending drug or drug combination, and effective alternatives usually are available.[146] Guidelines reviewing adverse events associated with specific antiretroviral drugs, classes, and combinations are regularly updated, and specific antiretroviral combinations associated with serious complications are not recommended.[14, 21] Serious or fatal non-obstetric adverse events appear rare on zidovudine monotherapy and currently recommended combination regimens.[186]

We identified one good-quality meta-analysis that found that zidovudine monotherapy in pregnant women did not cause any deaths or long-term maternal adverse events.[146] The largest prospective study examining obstetric adverse events from combination antiretroviral therapy

was an international study of 1,407 women that found that gestational diabetes was the only complication associated with antiretroviral therapy, and was most frequent for combination therapy that included a protease inhibitor and was initiated early in the pregnancy.[187] Other observational studies have also found an association between elevated serum glucose levels and protease inhibitor therapy in pregnant women.[188, 189] One recent clinical trial was discontinued after enrollment of 38 HIV-infected pregnant women because of a high rate of treatment-limiting hepatic or cutaneous toxicity with long-term nevirapine (29%) compared to nelfinavir (5%) in combination with zidovudine, including one death and one case of Stevens-Johnson syndrome.[148] Severe reactions to nevirapine were significantly more frequent in women with CD4 counts greater than 250 cells/mm^3. Observational studies (N=46-139) have also reported usually reversible hepatitis or abnormal liver function tests (1.1 to 5.0%) associated with long-term nevirapine that was rarely (2 cases) fatal.[190-192] No laboratory or clinical evidence of liver toxicity with single-dose intrapartum nevirapine, however, has been reported. Three recent randomized controlled trials of a single maternal intrapartum dose of nevirapine with or without other antiretroviral therapy found no differences in liver function tests or hepatitis between the nevirapine prophylaxis and the control group.[152, 158, 160]

Another potential harm of antiretrovirals initiated during pregnancy is the development of resistance or viral rebound, particularly in women who receive regimens that do not fully suppress viral replication or discontinue antiretrovirals after pregnancy.[52] Zidovudine monotherapy during the PACTG 076 trial, for example, was associated with an increased rate of low-level (but not high-level) genotypic zidovudine resistance.[130] Studies examining the effect of limited exposure to zidovudine monotherapy, however, did not find a negative impact on subsequent disease progression or response to later therapy.[53, 193, 194] In one of these studies, clinical benefits of HAART started in the postpartum period were comparable to those reported in other studies of persons without a recent pregnancy.[53] Lamivudine and zidovudine combination therapy was associated with lamivudine resistance mutations in 39% of treated pregnant women.[150]

Several recent studies examining the effects of single-dose intrapartum nevirapine prophylaxis have found nevirapine resistance mutations in 5%-32% of treated women six weeks postpartum.[65, 66, 131, 195] Of these studies, the only one that evaluated the clinical impact of these resistance mutations was a Thai trial that found that women who received single-dose intrapartum nevirapine in addition to standard zidovudine therapy were less likely to have complete virological suppression after six months of postpartum treatment with a nevirapine-containing regimen (49% vs. 68%).[131] CD4 cell count response and degree of weight loss, however, was not significantly different between groups receiving and not receiving nevirapine during pregnancy.

Maternal Harms of Elective Cesarean Section

HIV-infected women appear to be at increased risk for cesarean section-related complications than uninfected women. We identified two retrospective cohort studies that found that HIV-positive women had significantly more postoperative fever (OR 2.5-5.7) and minor complications such as urinary tract infections, endometritis, or wound infection (OR 2.7-3.1) compared to HIV-negative women.[196, 197] In one study, major adverse events (pneumonia, pleural effusion, transfusion, and sepsis) were reported in 6 of 156 HIV-infected patients.[197]

Cesarean section is generally associated with an increased risk of complications compared to vaginal delivery. We identified one randomized clinical trial that found that the rate of postpartum fever was 1.1% (2 of 183) in women delivering vaginally and 6.7% (15 of 225) for women delivering by cesarean section, but no serious postpartum complications occurred in either group.[171] We also identified two good-quality large prospective cohort studies[198, 199] and one retrospective cohort study[200] that evaluated the risk for HIV-infected women undergoing elective cesarean delivery versus vaginal delivery. The largest prospective study, with 1,186 HIV-infected women, found that elective cesarean section was associated with increased rates of postpartum fever (14.3%; RR 4.16, 95% CI 1.99-8.70), hemorrhage (7.1%; RR 1.58, 95% CI 0.58-4.26), endometritis (5.4%; RR 2.57, 95% CI 0.78-8.51), urinary tract infection (5.4%; RR 3.64, 95% CI 1.06-12.54), and any postpartum morbidity (26.7%; RR 2.62, 95% CI 1.61-4.20) compared to vaginal delivery.[199] Another prospective study (N=497) found that HIV-infected women delivering by cesarean section (elective or emergent) had an increased risk of endometritis (adjusted OR 4.8, 95% CI 2.5-9.3) and hemorrhage requiring blood transfusion (adjusted OR 2.8, 95% CI 1.0-8.4) compared to those delivering vaginally.[198] The retrospective study (N=309) found that HIV-infected women who delivered by elective cesarean section had more serious postpartum complications (fever, endometritis, urinary tract infection, pneumonia, wound infection, deep vein thrombosis [DVT], anemia requiring transfusion, transfer to intensive care, or death) than HIV-infected women who delivered vaginally (OR 1.85, 95% CI 1.00-3.39), but elective cesarean section was associated with fewer complications than emergency cesarean delivery.[200] An increased rate of postoperative complications was consistently associated with lower maternal CD4 count, and decreased rate with receipt of antiretrovirals and more recent year of delivery.

Harms of In Utero Antiretroviral Exposure to Infants

The Food and Drug Administration currently classifies didanosine, saquinavir, ritonavir, enfuvirtide, and nelfinavir as pregnancy class B (animal studies fail to demonstrate risk to the fetus and no human studies have been conducted).[201] Zidovudine, zalcitabine, stavudine, lamivudine, abacavir, indinavir, amprenavir, lopinavir, nevirapine, efavirenz, fosamprenivir and delavirdine are classified as pregnancy class C (safety in human pregnancy has not been determined). Use of efavirenz in early pregnancy is not recommended due to high rates of fetal anomalies in animal studies and case reports of adverse human pregnancy outcomes.[18]

HIV-seropositivity appears to be associated with an increased risk of perinatal and neonatal complications. A good-quality systematic review of 31 studies found that compared to HIV-negative women, HIV-positive women had significantly higher rates of spontaneous abortion (OR 4.05, 95% CI 2.75-5.96), stillbirth (OR 3.91, 95% CI 2.65-5.77), intrauterine growth retardation (OR 1.7, 95% CI 1.43-2.02), premature delivery (OR 1.83, 95% CI 1.63-2.06), and low birth weight infants (OR 2.09, 95% CI 1.86-2.35), but no significant increases in fetal abnormalities or neonatal mortality.[202]

We identified one good-quality U.S. meta-analysis of five prospective cohort studies and one good-quality, large European prospective cohort study that found no significant differences in the rates of congenital anomalies, neonatal conditions, or low birth weight between infants exposed to any combination of antiretroviral therapy and unexposed infants (Tables 13 and 14).[39, 203] On the other hand, data regarding the association between combination antiretroviral therapy and increased rates of premature delivery are mixed. The meta-analysis found no

increase in premature delivery rates for infants exposed to combination therapy with (OR 1.50, 95% CI 0.72-3.01) or without a protease inhibitor (OR 0.95, 95% CI 0.51-1.69) compared to no treatment,[203] but a large European prospective cohort study found an increased rate of premature birth associated with combination therapy (adjusted OR 2.60-4.14 for combination therapy with a protease inhibitor and 1.82-2.66 without a protease inhibitor compared to no treatment).[204]

Although molecular evidence of mitochondrial dysfunction has been reported in infants exposed in utero to antiretroviral therapy,[205, 206] the clinical impact of such dysfunction is unclear.[207, 208] A recent prospective Canadian observational study, for example, found that 92% of uninfected infants exposed to HAART in utero had elevated plasma lactate levels on at least one occasion, but none were clinically ill.[209] Large cohort studies have also found no evidence of clinical mitochondrial dysfunction among HIV-negative infants exposed to antiretroviral therapy.[39, 210] In population-based mortality studies, no deaths due to mitochondrial dysfunction among exposed, HIV-negative infants have been reported.[211-213]

Studies with longer duration of follow-up (four to six years) are so far available only for zidovudine monotherapy. We identified one good-quality meta-analysis and one good-quality prospective cohort study that found that in utero and postnatal zidovudine did not cause any increase in detectable long-term adverse clinical events or changes in growth or development in exposed infants up to four years of age.[146, 214] Zidovudine use also was not found to increase rates of prematurity or low birth weight. No tumors or deaths from cancers were reported among 727 children exposed to zidovudine in utero and followed for six years.[215]

Key Question 9. Have Improvements in Intermediate Outcomes (CD4 Counts, Viremia, or Risky Behaviors) in HIV-Infected Pregnant Women Been Shown to Improve Clinical Outcomes or Reduce Mother-to-Child Transmission?

Higher maternal viral loads and lower CD4 counts are associated with an increased risk of mother-to-child transmission of HIV.[29-35, 37, 39, 41, 49, 216-218] Observational studies and clinical trials have consistently found that women receiving highly active antiretroviral regimens who had a reduction in HIV RNA to <1,000 copies/ml had very low rates (about 1%) of perinatal transmission.[37, 150, 151, 173, 219]

Several maternal behaviors (such as unprotected intercourse,[46, 220] illicit drug use,[46, 221] or cigarette smoking[43, 222]) may be associated with an increased rate of vertical transmission, but we identified no studies evaluating the association between changes in these behaviors and subsequent rates of mother-to-child transmission.

Chapter 4. Discussion

Summary of Evidence

There is no direct evidence on benefits of screening for HIV infection in pregnant women. Other evidence obtained for the systematic review is summarized in Table 15. It indicates the study design and the quality of evidence for each key question. Briefly, universal screening identifies significantly more HIV-infected pregnant women than targeted screening. HIV tests are extremely accurate and recommended interventions markedly reduce the risk of mother-to-child transmission of HIV infection. Currently recommended interventions appear to be associated with high benefit-to-harm ratios.

Outcomes Table

Table 16 estimates the outcomes from screening prior to the third trimester in three hypothetical cohorts (0.15% prevalence, 0.30% prevalence, and high risk) of 10,000 pregnant women, using the highest quality and most applicable available evidence. We did not include areas in this table in which reliable data to estimate the clinical magnitude of benefit or harm were not available, such as harms from screening (anxiety, labeling, violence, suicide, partnership dissolution) or decreased horizontal transmission from counseling. We focused on the benefits of receipt of combination antiretroviral regimens on the risk of mother-to-child transmission, as this intervention has the greatest impact on transmission rates, and there were insufficient or limited data on other clinical outcomes (such as long-term maternal outcomes or horizontal transmission rates) or benefits associated with other interventions such as prophylaxis for opportunistic infections, counseling on risky behaviors, immunizations, routine monitoring and follow-up, or additional benefits from elective cesarean section in women receiving HAART. For harms of interventions, we focused on the rate of postpartum complications from elective cesarean section, as studies have not shown clear evidence of long-term infant adverse events from exposure to antiretrovirals, and there are insufficient data regarding the risks of antiretroviral exposure on long-term maternal outcomes. We calculated numbers needed to screen and treat to prevent one case of maternal-to-child transmission and cause one postpartum complication (postpartum fever, endometritis, hemorrhage, or urinary tract infection) from elective cesarean section (Appendix E).

To estimate the benefits of counseling and screening for HIV infection in pregnant women, we made several assumptions. We used recent estimates of rates of combination antiretroviral regimens (60%-90%)[37, 134-137] and elective cesarean section (37%-50%) utilization by HIV-infected pregnant women in the U.S.[134, 137, 138] Our estimates of the effectiveness of interventions were conservative and did not include potential benefits from elective cesarean section or avoidance of breastfeeding in women receiving combination therapy.[48] We also did not include potential benefits from screening on long-term maternal outcomes.

Numbers needed to screen to prevent one case of infant HIV infection ranged from 3,500 to 12,170 in the low-risk population to 105 to 365 in high-risk women. The number needed to treat with interventions to prevent one case of infant HIV infection was 4.3-9.9. The number needed to screen to cause one postpartum complication from elective cesarean section ranged from 4,280 to 31,640 in the low-risk population to 130 to 940 in the high-risk population. The number needed to treat to cause one postpartum complication from elective cesarean section was about 6 (95% CI, 2.9 to 15.9).

Conclusions

There are no published trials directly linking screening for HIV in pregnant women with clinical outcomes. In developed countries, the rate of mother-to-child transmission from untreated HIV-infected women ranges from 14% to 25%. Targeted screening of pregnant women with risk factor assessment would miss a significant proportion of infected persons. Standard office-based testing is highly (>99%) sensitive and specific, and initial studies of rapid HIV tests in labor and delivery settings found similar diagnostic accuracy. HIV testing rates during pregnancy continue to vary widely in the U.S. and appear to be higher in states using 'opt-out' testing policies. Recommended interventions (antiretroviral prophylaxis, elective cesarean section in selected patients, and avoidance of breastfeeding) are associated with transmission rates of 1%-2% in clinical trials and large observational studies. Shorter regimens are less effective, but also decrease the rate of transmission. The estimated benefits from combination antiretroviral regimens appear to greatly outweigh the risk of short-term complications, but long-term follow-up is not yet available. Elective cesarean section is associated with an increased risk of mostly short-term maternal adverse events. There are insufficient data to estimate the effects of interventions during pregnancy on long-term maternal disease progression or other outcomes (such as horizontal transmission).

Limitations of the Literature

In assessing the balance of benefits and harms from screening for HIV infection in pregnant women, we highlight several areas of key uncertainties.

Population Screened

Studies that have assessed the usefulness of risk factor assessment to guide screening were mostly performed before the CDC recommended universal counseling and voluntary prenatal HIV testing, but indicated that targeted screening missed a significant proportion of HIV-positive women. Even with universal counseling and voluntary testing policies, a significant minority of women remains untested. Studies evaluating programs to increase uptake rates in target groups such as adolescent minority women are lacking.

Currently recommended HIV counseling prior to testing and subsequent follow-up require substantial resources. More abbreviated or streamlined counseling methods (including opt-out

testing policies) might encourage more providers to offer screening and patients to accept it, but could also result in less informed choices by women, and require further study. There are also insufficient data regarding the usefulness of repeat screening in the third trimester in high- or low-risk women who tested negative earlier.

Screening Methods

Rapid serum testing of women with unknown HIV status presenting in labor appears to be an accurate and feasible method for quickly determining eligibility for urgent interventions. The effect of other sampling or testing methods (home-based sampling, urine or oral specimens, or on-site testing) on acceptance of testing and rates of patient notification of results have not been evaluated in pregnant women, but could be effective in women who receive limited or no prenatal care or who do not undergo standard office-based testing for other reasons.

Harms from Screening

Anecdotal reports of violence, suicide, partnership dissolution, and other adverse effects from screening are concerning, but data to estimate the magnitude of these harms are limited. Pregnant women may be particularly vulnerable to these adverse effects. Good-quality studies on methods to minimize the risk of these harmful outcomes are lacking.

Interventions

The combination of antiretroviral prophylaxis, elective cesarean section, and avoidance of breastfeeding is highly effective in reducing rates of mother-to-child transmission of HIV infection. Studies on long-term maternal and infant risks and benefits associated with different combination regimens, however, are not yet available. Further studies are needed to determine the optimal antiretroviral regimen, and whether elective cesarean section has an additive effect in women receiving HAART. The long-term effects of transient antiretroviral exposure or less-intense antiretroviral regimens during pregnancy on resistance rates and future response to therapy also need to be studied further. There are insufficient data regarding the effectiveness of counseling on rates of vertical or horizontal transmission, or on the effect that knowledge of HIV status has on future reproductive choices.

Future Research

Studies evaluating short and long-term effects of different antiretroviral regimens, particularly in women who do not otherwise meet criteria for initiation of HAART, are being conducted and will help clarify the optimal antiretroviral regimen choice during pregnancy. Longer-term follow-up studies of women and infants who received antiretrovirals are also being conducted and remain a priority. Particular attention should be paid to long-term outcomes in women who discontinued antiretrovirals after delivery to determine whether brief exposure affects future response rates or the choice of subsequent antiretroviral regimens. Children

exposed to antiretrovirals in utero should continue to be followed to help identify unexpected or emerging long-term harms from combination regimens.

Most studies of HIV-infected pregnant women have focused on benefits from reductions in mother-to-child transmission rates. Studies evaluating the effects of HIV diagnosis and counseling on future reproductive choices, high-risk behaviors, horizontal transmission rates, and other non-pregnancy-related outcomes could help to further strengthen the case for universal screening, particularly in low-risk populations.

Further studies of rapid tests and other new sampling and testing methods in office-based and outreach settings will help clarify their role in improving prenatal testing and notification rates. Studies evaluating methods to resolve barriers to testing remain a priority and include further evaluation on the impact of policy choices (such as opt-out testing or mandatory newborn screening) and different (such as streamlined or targeted) counseling methods on testing rates.

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Figure 1. Screening For Human Immunodeficiency Virus (HIV): Analytic Framework For Pregnant Women

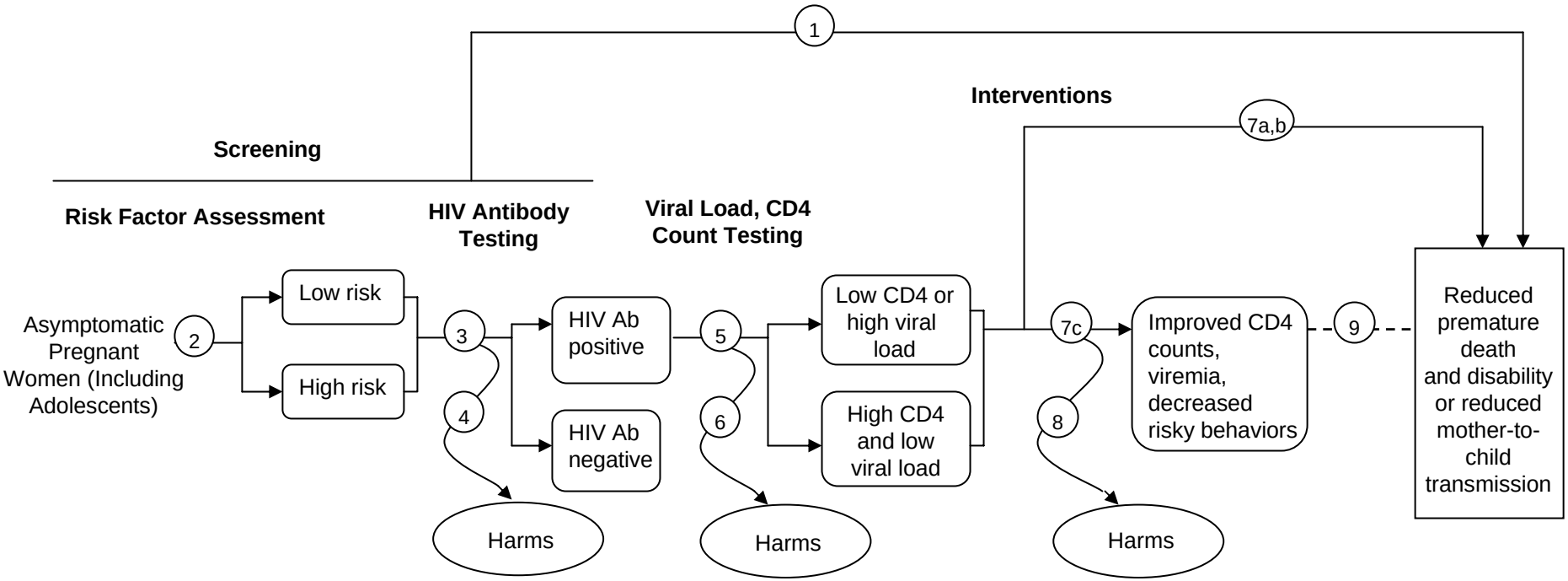

Figure 2. Screening for Human Immunodeficiency Virus (HIV): Key Questions for Pregnant Women Analytic Framework

KQ 1: Does screening for HIV in asymptomatic pregnant women reduce mother-to-child transmission or premature death and disability?

KQ 2: Can clinical or demographic characteristics (including persons in specific settings) identify subgroups of asymptomatic pregnant women at increased risk for HIV infection compared to the general population of pregnant women?

KQ 3: What are the test characteristics of HIV antibody test strategies in pregnant women?

KQ 4: What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to pregnant women?

KQ 5: How many HIV-infected pregnant women who meet criteria for interventions receive them?

KQ 6: What are the harms associated with the work-up for HIV infection in pregnant women?

KQ 7: a) How effective are interventions (antiretroviral prophylaxis [to prevent mother-to-child transmission] or treatment [to improve maternal outcomes], avoidance of breastfeeding, elective cesarean section [in selected patients] or other labor management practices, counseling on risky behaviors, immunizations, routine monitoring and follow-up or prophylaxis for opportunistic infections) in reducing transmission rates or improving clinical outcomes (mortality, functional status, quality of life, symptoms, or opportunistic infections) in pregnant women with HIV infection?

Figure 2. Screening for Human Immunodeficiency Virus (HIV): Key Questions for Pregnant Women Analytic Framework (continued)

b) Does immediate antiretroviral treatment in HIV-infected pregnant women result in improvements in clinical outcomes compared to delayed treatment until symptomatic?

c) How well do interventions reduce the rate of viremia, improve CD4 counts, and reduce risky behaviors? How does identification of HIV infection in pregnant women affect future reproductive choices?

KQ 8: What are the harms (including adverse effects from in utero exposure) associated with antiretroviral intervention and elective cesarean section?

KQ 9: Have improvements in intermediate outcomes (CD4 counts, viremia, or risky behaviors) in HIV-infected pregnant women been shown to improve clinical outcomes or reduce mother-to-child transmission?

Table 1. U.S. Guidelines For HIV Counseling And Testing In Pregnant Women

Organization	Year	Who to screen	Reference
US Preventive Services Task Force	1996	All high-risk pregnant women, including women living in states, counties or cities with a newborn prevalence of HIV infection >=0.1%.	USPSTF, 1996[56]
Centers for Disease Control and Prevention	2001	Universal screening of pregnant women during prenatal care or at time of presentation to labor & delivery if not already done with maternal right to refuse testing	CDC, 2001[18]
American Academy of Pediatrics	1995	Universal screening of pregnant women with maternal right to refuse testing	American Academy of Pediatrics, Provisional Committee on Pediatric AIDS, 1995[73]
American College of Obstetricians and Gynecologists	1999	Universal screening of pregnant women with maternal right to refuse testing	Joint Statement of AAP and ACOG, 1999[57]
Institute of Medicine	1999	Universal screening of pregnant women with maternal right to refuse testing	Institute of Medicine, 1999[58]

Table 2. Test Characteristics Of Rapid HIV-1 Antibody Tests Evaluated In Pregnant Women

Test	N	Sensitivity	Specificity	PPV	NPV	Quality	Source
OraQuick®	5744	100 (90-100)	99.9 (99.78-99.98)	90 (75-97)	100	GOOD	Bulterys et al, 2004[99]
Single Use Dignostic System (SUDS)	96	100	98	33	100	GOOD	Webber et al, 2001[100]
Capillus HIV-1/HIV-2	6655	99 (94-100)	98.9 (98.6-99.1)	58.1 (50.5-65.4)	100 (99.9-100)	GOOD	Ramalingam et al, 2002[101]
	347	100	100	98.98	100	FAIR. Inadequate description of patient population	Lien et al, 2000[103]
	1267	95.8	99.7	95.8	98.1	FAIR. Inadequate description of patient population	Mashu et al, 1997[104]
	1216	101 (99.13-100)	99.4 (98.71-99.86)			FAIR. Inadequate description of patient population; Western blot not included in gold standard	Koblavi-Deme et al, 2001[105]
Determine HIV-1/2	347	100	99.6	98.98	100	FAIR. Inadequate description of patient population	Lien et al, 2000[103]
	1216	101 (99.13-100)	99.7 (99.09-99.96)			FAIR. Inadequate description of patient population	Koblavi-Deme et al, 2001[105]

Table 2. Test Characteristics Of Rapid HIV-1 Antibody Tests Evaluated In Pregnant Women

Test	N	Sensitivity	Specificity	PPV	NPV	Quality	Source
	2152	100	99.85	97.54	100	FAIR. Inadequate description of patient population	Chalermchockcharoenkit et al, 2002[102]
Serodia HIV-1	347	100	100	100	100	FAIR. Inadequate description of patient population	Lien et al, 2000[103]
Multispot HIV-1/HIV-2	96	100	100	100	100	GOOD	Webber et al, 2001[100]
Genie II HIV-1/HIV-2	1216	100 (99.13-100)	99.7 (99.09-99.96)			FAIR. Inadequate description of patient population	Koblavi-Deme et al, 2001[105]
HIV-SPOT	1216	100 (98.9-100)	99.6 (99.29-99.99)			FAIR. Inadequate description of patient population	Koblavi-Deme et al+H10, 2001[105]

PPV, positive predictive value; NPV, negative predictive value. Blank cells indicate study was not designed to calculate this value.

Table 3. Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Iinfection

Study, year	Location	Interventions	Number enrolled (mother-infant pairs)	Mother-to-child transmission rate	Cesarean section rate	Breastfeeding rate	Internal validity rating
Italian Register, 2002[48]	Italy	A. No antiretrovirals B. ZDV monotherapy C. 2 or more drug therapy	A. 2,440 B. 743 C. 248	A. 18.5% B. 6.1% C. 1.6%	97.7% overall, 69.9% elective	2.8% overall	GOOD
Women and Infants Transmission Study, 2002[37]	US	A. No antiretrovirals B. ZDV monotherapy C. 2 drug therapy D. HAART	A. 396 B. 710 C. 186 D. 250	A. 20.0% B. 10.4% C. 3.8% D. 1.2%	A. 20.1% B. 24.0% C. 33.8% D. 44.4% p=0.0001	No infant was breastfed	GOOD
European Collaborative Study, 2005[149]	Europe	A. No antiretrovirals B. HAART	A. 157 B. 918	A. 11.5% B. 1.2%	16% emergency, 61% elective	2% overall (through 2000)	GOOD
French Perinatal Study (Mandelbrot et al, 2001)[150]	France	A. ZDV monotherapy (historical control group) B. Lamivudine + ZDV from 32 weeks in pregnancy and to the child for 6 weeks	A. 858 B. 437	A. 6.8% B. 1.6%	A: 16% elective B: 22% elective	A. 0.3% B. 0.5%	FAIR. Used historical controls

HAART, highly active antiretroviral therapy; ZDV, zidovudine.

Table 4. Evidence Table: Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Infection

Author, year	Study name, location	Type of study	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)
European Collaborative Study, 2005[149]	Europe	Prospective cohort	To describe changes in characteristics and management of HIV-positive women in Europe over time	1983-2004	HIV positive	Mom in study
Cooper et al, 2002[37]	Women and Infants Transmission Study, US	Prospective cohort study	To evaluate the impact of different antiretroviral therapy regimens on mother-to-child transmission of HIV on the population level	Jan 1990-June 2000	Singleton live birth in study period, HIV positive	Mom in study

Table 4. Evidence Table: Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Infection

Author, year	Number enrolled	Population characteristics	Treatment	Cesarean rate	Breastfeeding rate
European Collaborative Study, 2005[149]	A: 157 B: 918	Average maternal age 30.7, 10% had CD4 count <200 cells/mm^3	A. No antiretroviral therapy B. HAART	16% emergency, 61% elective	2% overall breastfeeding rate (through 2000)
Cooper et al, 2002[37]	A. 396 B. 710 C. 186 D. 250	81% minority, median age at delivery 27.8, 31% drug users	A. No anti-retroviral therapy B. ZDV monotherapy C. 2 or more drug therapy D. HAART	A. 20.1% B. 24.0% C. 33.8% D. 44.4% p=0.0001	No infant was breastfed

Table 4. Evidence Table: Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Infection

Author, year	Transmission rate	Other risk factors associated with mother-to-child transmission	Adverse events	Comments	Internal validity rating
European Collaborative Study, 2005[149]	A. 11.5% B. 1.2%	Elective cesarean section decreased risk of transmission, AOR 0.38 (95% CI 0.24 to 0.61) compared to vaginal delivery	Antiretroviral treatment associated with reversible anemia in the newborn; no pattern of congenital abnormalities seen with antiretroviral treatment (data reported in earlier study)	Data reported for women enrolled in the HAART era (1997-2004)	GOOD
Cooper et al, 2002[37]	A. 20.0% B. 10.4% C. 3.8% D. 1.2% Multi-drug therapy vs. ZDV monotherapy OR 0.30 (0.09-1.02) HAART vs. ZDV monotherapy OR 0.27 (0.08-0.94)	Duration of membrane rupture >4 hours increased risk of transmission OR 1.70 (1.00-2.90) Maternal plasma HIV RNA levels at delivery increased risk of tranmission per 1 log10 increment rise (copies/mL) OR 2.42 (1.69-3.46)	Rates of preterm and low birth weight infants did not significantly vary by type of antiretroviral therapy; however, both rates were lower than rates for women receiving no antiretroviral therapy.	Significantly more women receiving antiretroviral therapy had elective cesarean section; elective cesarean section significantly lowered rate of mother-to-child transmission vs. vaginal delivery (1.6% vs. 8.4%, p=0.006) for women on antiretroviral therapy.	GOOD

Table 4. Evidence Table: Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Infection

Author, year	Study name, location	Type of study	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)
Mandelbrot et al, 2001[150]	French Perinatal Study, France	Prospective cohort with historical controls	To determine the safety and efficacy of lamivudine treatment in addition to standard ZDV for decreasing mother-to-child transmission	Feb. 1997-Sept. 1998 for study, May 1994-Feb. 1997 for controls	HIV positive	Mom in study
Italian Register For HIV Infection in Children, 2002[48]	Italian	Prospective observational	To determine the risk factors for mother-to-child transmission for HIV	1985-1995 cohort and 1996-1999 cohort	HIV positive	Reported to register

AOR, adjusted odds ratio; HAART, highly active antiretroviral therapy; ZDV, zidovudine.

Table 4. Evidence Table: Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Infection

Author, year	Number enrolled	Population characteristics	Treatment	Cesarean rate	Breastfeeding rate
Mandelbrot et al, 2001[150]	Study: 445 mother-infant pairs Historical control: 899 mother-infant pairs	Median age 30 years, 11% history of intravenous drug abuse, 50% born in sub-Saharan Africa, median CD4 cell count at enrollment: Study: 426 cells/microL Control: 436 cells/microL	Study: lamivudine from 32 weeks gestation through delivery in addition to ZDV standard protocol Control: ZDV using 076 protocol	Study: 37% (22% elective) Control: Not given (16% elective) Elective cesarean section p=0.005	Study: 0.5% Control: 0.3%
Italian Register For HIV Infection in Children, 2002[48]	A. 2,440 B. 743 C. 248	64.1% intravenous drug users	A. No treatment B. ZDV monotherapy C. 2 or more antiretroviral therapy	97.7% overall cesarean rate	2.8% overall breastfeeding rate

AOR, adjusted odds ratio; HAART, highly active antiretroviral therapy; ZDV, zidovudine.

Table 4. Evidence Table: Large Observational Cohort Studies Of Combination Antiretroviral Regimens On Risk Of Mother-to-Child Transmission Of HIV Infection

Author, year	Transmission rate	Other risk factors associated with mother-to-child transmission	Adverse events	Comments	Internal validity rating
Mandelbrot et al, 2001[150]	Study: 1.6% Control: 6.8% AOR for lamivudine + ZDV vs. ZDV monotherapy: 0.22 (0.10-0.50)	AOR for elective cesarean section increased risk of transmission vs. other types of delivery 0.30 (0.09-0.99) Advanced maternal HIV disease increased risk of transmission OR 2.30 (1.25-4.22) Prior antiretroviral treatment increased risk of transmission OR 2.22 (1.15-4.28)	Significant increase in low hemoglobin level (p=0.004) and low neutrophil count (p<0.001) in babies with lamivudine treatment	Lamivudine + ZDV reduced HIV viral load to less than detectable at delivery in 74% of study group	FAIR Historical controls
Italian Register For HIV Infection in Children, 2002[48]	A. 18.5% B. 6.1% C. 1.6% AOR for 2 or more drug therapy vs. no treatment 0.07 (0.02-0.23)	Breastfeeding increased risk of transmission OR 10.20 (2.73-38.11)	Not reported		GOOD

AOR, adjusted odds ratio; HAART, highly active antiretroviral therapy; ZDV, zidovudine.

Table 5. Number of Drugs in Full-course Antiretroviral Regimens and Risk of Mother-to-Child Transmission of HIV Infection

Antiretroviral regimen comparison	Risk of mother-to-child transmission	Source	Type of study
Zidovudine alone (complete PACTG 076) vs. placebo	RR 0.32 (0.18-0.59)	Connor et al, 1994[83]	Randomized controlled trial
	AOR 0.12 (0.05-0.30)	Italian Register, 2002[48]	Prospective cohort
One or two drugs vs. no antiretrovirals	AOR 0.49 (0.31-0.76)	European Collaborative Study, 2005[149]	Prospective cohort
Two or more drugs vs. no antiretrovirals	AOR 0.07 (0.02-0.23)	Italian Register, 2002[48]	Prospective cohort
HAART vs. no antiretrovirals	AOR 0.13 (0.06-0.27)	European Collaborative Study, 2005[149]	Prospective cohort
Two or more drugs vs. zidovudine alone	AOR 0.22 (0.10-0.59)	Mandelbrot et al, 2001[150]	Cohort with historical controls
	AOR 0.30 (0.09-1.02)	Cooper et al, 2002[37]	Prospective cohort
HAART vs. zidovudine alone	AOR 0.27 (0.08-0.94)	Cooper et al, 2002[37]	Prospective cohort

AOR, adjusted odds ratio; HAART, highly active antiretroviral therapy; PACTG, Pediatric AIDS Clinical Trials Group; RR, relative risk.

Table 6. Randomized Controlled Trials ofLonger (Before 34 Weeks Gestation) Antiretroviral Regimens for Reduction of Mother-to-Child Transmission of HIV Infection in Non-breastfeeding Women

Study, year	Location	Interventions	Number in trial (mother-child pairs)	Mother-to-child transmission rate	Cesarean section rate	Internal validity rating
PACTG 076 (Connor et al, 1994)[83]	US	A. Zidovudine from 14-34 weeks gestation, intrapartum and postpartum to infant B. Placebo	A. 180 B. 183	A. 8.3% B. 25.5%	A. 41.6% B. 33.7%	GOOD
PACTG 316 (Dorenbaum et al, 2002)[151]	US, Europe, Brazil, and the Bahamas	A. Usual antiretroviral treatment + placebo B. Usual antiretroviral treatment + nevirapine intrapartum + nevirapine to the newborn (77% on combination therapy)	A. 628 B. 642	A. 1.6% B. 1.4%	A. 53.1% B. 49.8%	GOOD
Perinatal HIV Prevention Trial (Lallemant et al, 2004)[152]	Thailand	A. Standard zidovudine + nevirapine intrapartum + nevirapine to the newborn B. Standard zidovudine + nevirapine intrapartum C. Standard zidovudine	A. 636 B. 628 C. 316	A. 1.9% B. 2.8% C. 6.3%	A. 19.2% B. 22.5% C. 21.3%	GOOD

Table 7. Evidence Table: Randomized Controlled Trials of Longer (Before 34 Weeks Gestation) Courses of Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection in Non-Breastfeeding Women

Study name, author, year	Location	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)
Perinatal HIV Prevention Trial Lallemant et al, 2004[152]	Thailand	To determine the effect of adding perinatal nevirapine therapy to standard ZDV therapy in prevention of vertical transmission of HIV	Jan 15, 2001-Feb 28, 2003	HIV positive, receiving standard ZDV prophylaxis, agree not to breastfeed. Normal kidney and liver function and normal hematologic parameters	Mom in study
PACTG 316 Dorenbaum et al, 2002[151]	Multi-national	To determine whether a two-dose nevirapine regimen decreases mother-to-child transmission of HIV in women receiving antiretroviral therapy	May 1997-June 2000	HIV positive, 13 or older, at least 28 weeks gestation at enrollment	Mom in study
PACTG 076 Connor et al, 1994[83]	US	Determine the efficacy and safety of ZDV in reducing the risk of mother-to-child HIV transmission	April 1991-Dec 1993	HIV positive, 14-34 weeks gestation, CD4 count >200 cells/microL, normal kidney and liver function	Mom in study

HAART, highly active antiretroviral therapy; ZDV zidovudine.

Table 7. Evidence Table: Randomized Controlled Trials of Longer (Before 34 Weeks Gestation) Courses of Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection in Non-Breastfeeding Women

Study name, author, year	Exclusion criteria (mother)	Exclusion criteria (baby)	Screened/eligible/ enrolled	Withdrawals or lost to follow-up/% analyzed
Perinatal HIV Prevention Trial Lallemant et al, 2004[152]	Breastfed, maternal or fetal condition or concomitant treatment that contraindicated treament with ZDV or nevirapine, oligohydramnios, unexplained polyhydramnios or in utero anemia, or medical condition that required immediate use of HAART	Stillborn, HIV status not known	3,061 screened, 1,844 randomized, 1,807 followed to delivery Randomized: A. 724 B. 721 C. 360	34 lost to follow-up, 10 stillbirths, 37 with insufficient data. Mother baby pairs analyzed: A. 693 B. 672 C. 348
PACTG 316 Dorenbaum et al, 2002[151]	Enrolled in prior study, had been previously treated with non-nucleoside reverse transcriptase inhibitors, hypersensitivity to benzodiazepine, elevated serum alanine amino-transferase, intention to breastfeed, lethal fetal anomaly	HIV status not known	A: 754 randomized B: 752 randomized	A. 123 excluded or lost to follow-up; 631 analyzed B.135 excluded or lost to follow-up; 617 analyzed
PACTG 076 Connor et al, 1994[83]	Serious fetal anomaly, previous antiretroviral treatment during this pregnancy, oligohydramnios in the second trimester, polyhydramnios In the third trimester	Lack of maternal consent to test infant, hyperbilirubinemia requiring more than phototherapy, abnormal hematologic parameters, abnormal liver function tests	477 women/415 infants A. 239 B. 238	12 lost to follow-up, 70 excluded A. 180 B. 183

HAART, highly active antiretroviral therapy; ZDV zidovudine.

Table 7. Evidence Table: Randomized Controlled Trials of Longer (Before 34 Weeks Gestation) Courses of Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection in Non-Breastfeeding Women

Study name, author, year	Population characteristics	Treatment	Cesarean rate	Breastfeeding rate	Transmission rate
Perinatal HIV Prevention Trial Lallemant et al, 2004[152]	Median age 26, median length of gestation at entry 31 weeks, median CD4 cell count (cells/mm3): A. 371 B. 373 C. 372	A. Standard ZDV + single dose nevirapine intrapartum + single dose nevirapine to newborn B. Standard ZDV + single dose nevirapine intrapartum C. Standard ZDV	A. 19.2% B. 22.5% C. 21.3%	No infants breastfed	A. 1.9% B. 2.8% C. 6.5%
PACTG 316 Dorenbaum et al, 2002[151]	Median age 28, median gestational age at entry 34 weeks, median CD4 cell count at entry (cells/mm3): A. 441 B. 423	A: Nevirapine intrapartum and one dose to newborn; previous antiretroviral therapy continued B: placebo plus previous antiretroviral therapy	A. 53.1% B. 49.8%	No infants breastfed	A: 1.4% B: 1.6%
PACTG 076 Connor et al, 1994[83]	Median age 25, median CD4 cell count at entry (cells/mm3): A. 560 B. 538	A. ZDV from 14-34 weeks gestation, intrapartum and postpartum to infant B. Placebo	A. 41.6% B. 33.7%	No infants breastfed	A. 8.3% B. 25.5%

HAART, highly active antiretroviral therapy; ZDV zidovudine.

Table 7. Evidence Table: Randomized Controlled Trials of Longer (Before 34 Weeks Gestation) Courses of Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection in Non-Breastfeeding Women

Study name, author, year	Other risk factors for mother-to-child transmission	Adverse events	Internal validity rating
Perinatal HIV Prevention Trial Lallemant et al, 2004[152]	Not reported	No significant difference in significant clinical or laboratory maternal or infant adverse events between treatment and placebo groups	GOOD
PACTG 316 Dorenbaum et al, 2002[151]	Low CD4 counts at baseline (<200 cells/mm3) increased risk of transmission (3.4% vs. 0.8%, p=0.03); HIV RNA level 400 copies /ml or higher increased rate of transmission (2.9% vs. 0.3%, p<0.001)	No significant difference in significant clinical or laboratory maternal or infant adverse events between treatment and placebo groups	GOOD
PACTG 076 Connor et al, 1994[83]	Not reported	No significant difference in significant clinical or laboratory maternal adverse events between treatment and placebo groups. Infants in the ZDV group had significantly lower hemoglobin levels at birth than infants in the placebo group.	GOOD

HAART, highly active antiretroviral therapy;
ZDV zidovudine.

Table 8. Randomized Controlled Trials of Short-Course Antiretroviral Regimens for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Location	Interventions	Number in trial (mother-child pairs)	Mother-to-child transmission rate	Cesarean section rate	Breastfeeding rate	Internal validity rating
Short-course zidovudine (ZDV) trials							
Bangkok Trial Shaffer et al, 1999[154]	Thailand	A. ZDV from 36 weeks and intrapartum B. Placebo	A. 194 B. 198	A. 9.4% B. 18.9% At 6 months p=0.006	A. 16% B. 12% p=0.2	A. 0% B. 0%	GOOD
Ivory Coast Trial Wiktor et al, 1999[156]	Africa	A. ZDV from 36 weeks gestation and intrapartum B. Placebo	A. 115 B. 115	A. 16.5% B. 26.1% 3 months	A. 1% B. 1%	A. 100% B. 100%	GOOD
DITRAME Dabis et al, 1999[157]	Africa	A. ZDV from 36-38 weeks gestation, intrapartum and to the baby for 7 days postpartum B. Placebo	A. 192 B. 197	A. 18.0% B. 27.5% At 6 months p=0.027	A. 3.0% B. 1.9% p=0.50	A. 100% B. 100%	GOOD
Perinatal HIV Prevention Trial Lallemant et al, 2000[153]	Thailand	A. ZDV from 26 weeks gestation, intrapartum and to infant for 6 weeks B. ZDV from 26 weeks gestation, intrapartum and to the infant for 3 days C. ZDV from 35 weeks gestation, intrapartum and to infant for 6 weeks D. ZDV from 35 weeks gestation, intrapartum, and to the infant for 3 days	A. 401 B. 340 C. 338 D. 229	A. 6.5% B. 4.7% C. 8.6% D. 10.5% Note: D stopped at first interim analysis when rate for A was 4.1% vs. 10.5%, p=0.004 No significant differences between A, B, and C	A. 18% B. 19% C. 17% D. 17%	A. 0% B. 0% C. 0% D. 0%	GOOD

Table 8. Randomized Controlled Trials of Short-Course Antiretroviral Regimens for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Location	Interventions	Number in trial (mother-child pairs)	Mother-to-child transmission rate	Cesarean section rate	Breastfeeding rate	Internal validity rating
Short-course combination regimens							
PETRA PETRA Study Group, 2002[155]	Africa	A. ZDV + lamivudine from 36 weeks gestation, intrapartum and postpartum B. ZDV + lamivudine intrapartum and postpartum C. ZDV + lamivudine intrapartum D. placebo	A. 281 B. 269 C. 281 D. 262	A. 5.7% B. 8.9% C. 14.2% D. 15.3% At 6 weeks OR vs. placebo A. 0.37 [0.21-0.65] B. 0.58 [0.36-0.94] C. 0.93 [0.62-1.40 D. 1.0	A. 33% B. 35% C. 32% D. 33%	A. 74% B. 73% C. 76% D. 74% At birth	GOOD
SAINT Moodley et al, 2003[158]	Africa	A. Nevirapine intrapartum and for the baby until 48 hours old B. Short course ZDV + lamivudine intrapartum and for the baby until 7 days old	A. 477 B. 467	A: 12.3% B: 9.3% At 8 weeks after delivery NS	A. 27.8% B. 31.4% NS	A. 46.2% B. 47.7% Ever breastfed	GOOD Open-label
NZAV Taha et al, 2003[159]	Africa	A. Nevirapine for infant after delivery B. Single dose nevirapine + ZDV for infant after delivery and ZDV for 1 week after delivery	A. 468 B. 484	A. 20.9% B. 15.3% At 6-8 weeks of age p=0.03	A. 0.7% B. 0.5% NS	A. 99.8% B. 99.6% At 1 week	GOOD Open-label
HIVNET 012 Jackson et al, 2003[160] Guay et al, 1999[162]	Africa	A. Nevirapine intrapartum and to newborn B. ZDV intrapartum and to newborn	A. 302 B. 308	A. 11.8% B. 20.0% At 6-8 weeks of age p=0.006	A. 11.5% B. 13.9% p=0.38	A. 99.3% B. 98.7% At birth p=0.40	GOOD Open-label

Table 8. Randomized Controlled Trials of Short-Course Antiretroviral Regimens for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Location	Interventions	Number in trial (mother-child pairs)	Mother-to-child transmission rate	Cesarean section rate	Breastfeeding rate	Internal validity rating
Taha et al, 2004[161]	Africa	A. Single oral dose of nevirapine intrapartum and single oral dose of nevirapine to infant B. Single oral dose of nevirapine intrapartum and single oral dose of nevirapine plus ZDV for 1 week to infant	A. 389 B. 408	A. 6.5% B. 6.9% At 6-8 weeks	A. 3.5% B. 1.1%	A. 99.2% B. 100% At 1 week	GOOD Open-label

NS, not significant.

Table 9. Evidence Table: Randomized Controlled Trials of Short Courses of Zidovudine (ZDV) Monotherapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Location	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)
Bangkok Trial Shaffer et al, 1999[154]	Thailand	To determine the safety and efficacy of short-course ZDV administered during late pregnancy and intrapartum	May 96-Dec. 97	HIV positive, 18 years old or older at delivery, at 34 weeks or less gestation at study enrollment, lived in or near Bangkok, intended to deliver in the study hospital, intended to not breastfeed, normal kidney and liver function, normal hematologic testing, able to give informed consent	Mom in study
Ivory Coast Trial Wiktor et al, 1999[156]	Africa	To evaluate the safety and efficacy of short-course ZDV in breastfeeding women on mother-to-child transmission of HIV	April 96-Feb. 98	HIV positive, at least 18 years of age, at less than 34 weeks estimated gestational age at enrollment, normal kidney and liver function, and normal blood counts	Mom in study
DITRAME study Dabis et al, 1999[157]	Africa	To assess the efficacy of short-course ZDV in breastfeeding women on mother-to-child transmission of HIV	Sept. 95-Feb. 98	HIV positive, at least 18 years of age, presented for care before 32 weeks gestation, normal blood counts, normal kidney and liver function	Mom in study
Perinatal HIV Prevention Trial Lallemant et al, 2000[153]	Thailand	To determine the optimal duration of ZDV administration to prevent perinatal transmission of HIV in areas with limited resources	June 24, 1997-Dec. 2, 1999	HIV positive, at 28 weeks gestation at enrollment, agreed not to breastfeed, normal blood counts, normal kidney and liver function	Mom in study

ZDV, zidovudine.

Table 9. Evidence Table: Randomized Controlled Trials of Short Courses of Zidovudine (ZDV) Monotherapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Exclusion criteria (mother)	Exclusion criteria (baby)	Screened/eligible/ enrolled	Withdrawals or lost to follow up/% analyzed	Population characteristics
Bangkok Trial Shaffer et al, 1999[154]	Intolerance to ZDV, known fetal anomalies, previous use of antiretroviral therapy, amniocentesis during the current pregnancy	HIV status not known	1,140 screened, 429 enrolled, 397 randomized	5 lost to follow-up, 12 excluded A. 194 B. 198	Median age 24, <1% intravenous drug users, CD4 count <200 cells/mm^3: A. 10% B. 12%
Ivory Coast Trial Wiktor et al, 1999[156]	Previous antiretroviral therapy, congenital anomalies, severe obstetric conditions	HIV status not known	17,046 screened, 982 eligible, 280 randomized	7 lost to follow-up, 43 excluded A. 139 B. 137	Median age 25-26 CD4 count <200 cells/mm^3: A. 7% B. 5%
DITRAME study Dabis et al, 1999[157]	Sickle cell anemia	HIV status not known	17,195 screened, 872 eligible, 431 randomized	14 lost to follow-up, 28 excluded A. 192 B. 197	CD4 count <200 cells/$mm^{3:}$ A. 8.3% B. 8.2%
Perinatal HIV Prevention Trial Lallemant et al, 2000[153]	Maternal or fetal condition or concomitant treatment contraindicating treatment with ZDV, oligohydramnios, unexplained hydramnios, in utero anemia	HIV status not known	1,114 women enrolled	20 lost to follow-up, 18 excluded A. 401 B. 340 C. 338 D. 229	Median age 24-25 CD4 count <200 cells/mm^3: A. 17% B. 20% C. 19% D. 20%

ZDV, zidovudine.

Table 9. Evidence Table: Randomized Controlled Trials of Short Courses of Zidovudine (ZDV) Monotherapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Treatment	Cesarean rate	Breastfeeding rate	Transmission rate
Bangkok Trial Shaffer et al, 1999[154]	A. ZDV from 36 weeks and intrapartum B. Placebo	A. 16% B. 12%	No participant breastfed	A. 9.4% B. 18.9% At 6 months p=0.006
Ivory Coast Trial Wiktor et al, 1999[156]	A. ZDV from 36 weeks and intrapartum B. Placebo	A. 1% B. 1%	100% breastfed	A. 16.5% B. 26.1% At 3 months p=0.07
DITRAME study Dabis et al, 1999[157]	A. ZDV from 36-38 weeks gestation, intrapartum and to the baby for 7 days postpartum B. Placebo	A. 3.0% B. 1.9% p=0.50	100% breastfed	A. 18.0% B. 27.5% At 6 months p=0.027
Perinatal HIV Prevention Trial Lallemant et al, 2000[153]	A. ZDV from 26 weeks gestation, intrapartum and to infant for 6 weeks B. ZDV from 26 weeks gestation, intrapartum and to the infant for 3 days C. ZDV from 35 weeks gestation, intrapartum and to infant for 6 weeks D. ZDV from 35 weeks gestation, intrapartum, and to the infant for 3 days	A. 18% B. 19% C. 17% D. 17%	No participant breastfed	A. 6.5% B. 4.7% C. 8.6% D. 10.5% Note: D stopped at first interim analysis A. 4.1% vs. D. 10.5%, p=0.004 No significant differences between A, B, and C

ZDV, zidovudine.

Table 9. Evidence Table: Randomized Controlled Trials of Short Courses of Zidovudine (ZDV) Monotherapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Other risk factors associated with mother-to-child transmission	Adverse events	Internal validity rating
Bangkok Trial Shaffer et al, 1999[154]	Lower CD4 counts increased rate of transmission (p=0.03) Viral HIV RNA plasma concentrations >10,000 copies/ml increased rate of transmission (p<0.005)	No significant difference between study and placebo groups	GOOD
Ivory Coast Trial Wiktor et al, 1999[156]	Maternal CD4 count not significant	Rates of severe maternal adverse events similar in both groups. Rates of congenital anomalies and severe laboratory abnormalities similar between groups. Significantly more infants in the placebo group died at <2 days (p=0.04) and between 2-120 days of life (p=0.008).	GOOD
DITRAME study Dabis et al, 1999[157]	Prolonged rupture of membranes (>4 hours) increased rate of transmission (p=0.015) Lower maternal CD4 count at entry increased rate of transmission (p=0.0004 for a decrease of 100 cells/mm^3)	No significant difference in major biological or clinical events between study and control groups	GOOD
Perinatal HIV Prevention Trial Lallemant et al, 2000[153]	Not reported	Rates of severe maternal adverse events similar in all groups. Transiently lower hemoglobin levels in infants of mothers who received long-course ZDV. Rates of serious infant adverse events were similar in all groups.	GOOD

ZDV, zidovudine.

Table 10. Evidence Table: Randomized Controlled Trials of Short Courses of Combination Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Location	Aims	Study duration	Eligibility criteria, mom	Eligibility criteria, baby	Exclusion criteria, mom
HIVNET 012 Jackson et al, 2003[160] Guay et al, 1999[162]	Africa	To determine the efficacy of intrapartum and newborn treatment with nevirapine vs. ZDV in reduction of mother-to-child transmission of HIV	Nov. 3, 1997-April 30, 1999	HIV positive, at least 18 years of age; at more than 32 weeks gestation at enrollment, and lived within 15 km of Mulago Hospital, normal kidney and liver function, normal hematological parameters	Mom in study, firstborn	Current antiretroviral or HIV-1 immunotherapy; uncontrolled hypertension; chronic alcohol or illicit drug use; and receipt of benzodiazepines, anticoagulant therapy, or magnesium sulfate within 2 weeks of enrollment or would require them during labor or at delivery
NVAZ Taha et al, 2003[159]	Africa	To determine whether post-exposure prophylaxis of nevirapine plus ZDV given to newborns reduced mother-to-child transmission of HIV compared to nevirapine alone	April 2000-Jan. 2002	Unknown HIV status when presenting in advanced labor, HIV positive at delivery	Mother HIV positive, singleton, not preterm	Receipt of predelivery antiretroviral treatment
SAINT Moodley et al, 2003[158]	Africa	To determine the efficacy and safety of 2 antiretroviral therapy regimens for prevention of mother-to-child transmission of HIV	May 1999-Feb. 2000	HIV positive, agree to randomization, >16, >38 weeks gestation at presentation in latent or active labor	Mom in study	Elective cesarean section planned, life-threatening obstetrical complications

Table 10. Evidence Table: Randomized Controlled Trials of Short Courses of Combination Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Exclusion criteria, baby	Screened/eligible/ enrolled	Withdrawals or lost of follow-up/% analyzed	Population characteristics	Treatment	Cesarean rate
HIVNET 012 Jackson et al, 2003[160] Guay et al, 1999[162]	HIV status not known	13,839 screened, 2,144 eligible, 645 enrolled Randomized: A. 313 B. 313 C. 19 (discontinued arm)	10 lost to follow-up, 7 with insufficient data Analyzed: A. 308 B. 302	Median age A. 24, B. 25 Median CD4 count (cells/microL): A. 459 B. 426	A. Nevirapine orally as a single dose intrapartum and to newborn B. ZDV orally intrapartum and to newborn for 7 days	A. 11.5% B. 13.9%
NVAZ Taha et al, 2003[159]	Low Apgar score, condition requiring admission to neonatal intensive care unit, HIV positive at birth	12,355 screened, 1,119 randomized	119 infants excluded, 135 lost to follow-up Analyzed: A. 444 B. 421	Median maternal age 25 Median CD4 count not reported	A. Single dose of nevirapine to newborn B. Single dose of nevirapine and of ZDV to newborn, ZDV for 1 week	A. 0.7% B. 0.5%
SAINT Moodley et al, 2003[158]	HIV status not known	1,373 screened A: 662 randomized B: 657 randomized	390 lost to follow-up Analyzed: A: 477 B. 467	Median age at entry 25, median CD4 count (cells/microL): A. 404.5 B. 384.5	A: Nevirapine in labor and postpartum for 48 hours B: ZDV/3TC in labor and 1 week postpartum	A. 27.8% B. 31.4%

Table 10. Evidence Table: Randomized Controlled Trials of Short Courses of Combination Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Breastfeeding rate	Transmission rate	Other risk factors associated with mother-to-child transmission	Adverse events	Internal validity rating
HIVNET 012 Jackson et al, 2003[160] Guay et al, 1999[162]	A. 99.3% B. 98.7% At birth	A. 11.8% B. 20.0% At 6 weeks	Maternal HIV RNA level at entry increased rate, for each unit increase of log OR 1.81 (1.36-2.40); maternal CD4 count at entry increased rate, for each decrease of 100 cells/microliter OR 1.19 (1.09-1.31)	No significant difference in rates of serious adverse events in mothers or infants between treatment groups	GOOD Open label
NVAZ Taha et al, 2003[159]	A. 99.8% B. 99.6% At 1 week	A. 20.9% B. 15.3% At 6-8 weeks of age p=0.03	Maternal viral load (per log 10 increase) increased rate OR 3.18 (2.08-4.63)	No significant differences in adverse events between groups	GOOD Open label
SAINT Moodley et al, 2003[158]	A. 46.2% B. 47.7% Ever breastfed	A: 5.7% B: 3.6% At 8 weeks postpartum	Breastfeeding at 4-8 weeks increased rate OR 7.23 (2.06-25.34) Baseline maternal HIV RNA level >50,000 copes/mL increased rate OR 2.9 (1.8-4.8) Maternal antiretroviral dose <2 hours prior to delivery increased rate OR 3.1 (1.4-7.1) Emergency cesarean section increased rate OR 2.5 (1.1-5.6)	No significant difference in rates of serious adverse events in mothers or infants between treatment groups	GOOD Open label

Table 10. Evidence Table: Randomized Controlled Trials of Short Courses of Combination Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Location	Aims	Study duration	Eligibility criteria, mom	Eligibility criteria, baby	Exclusion criteria, mom
PETRA PETRA Study Team, 2002[155]	Africa	To assess the efficacy of short-course regimens with ZDV and 3TC	June 1996-Feb. 1998	HIV positive, agree to randomization, older than 18 years of age or legal age of consent, ability to give informed consent, less than 36 weeks gestation at enrollment, absence of severe fetal anomalies, absence of life-threatening disease, normal hemoglobin, 18 month follow-up possible	Mom in study	Died
NVAZ Taha et al, 2004[161]	Africa	To determine the risk of mother-to-child transmission of HIV with nevirapine alone or with ZDV administered intrapartum and to infants after delivery	April 2000-March 2003	Presented to labor ward more than 4 hours prior to delivery, able to provide informed consent, HIV positive	Mom in study	Confirmatory ELISA test negative

ELISA, enzyme-linked immunoabsorbent assay; 3TC, lamivudine; ZDV, zidovudine.

Table 10. Evidence Table: Randomized Controlled Trials of Short Courses of Combination Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Exclusion criteria, baby	Screened/eligible/ enrolled	Withdrawals or lost of follow-up/% analyzed	Population characteristics	Treatment	Cesarean rate
PETRA PETRA Study Team, 2002[155]	HIV status not known	4,640 screened; A. 366 randomized B. 371 randomized C. 368 randomized D. 352 randomized	A. 84 lost to follow-up, 268 analyzed B. 120 lost to follow-up, 251 analyzed C. 113 lost to follow-up, 255 analyzed D. 99 lost to follow-up, 253 analyzed	Median age 26, median CD4 count (cells/microL): A. 445 B. 475 C. 440 D. 435	A: ZDV + 3TC at 36 weeks, intrapartum and 7 days postpartum B: ZDV and 3TC intrapartum and 7 days postpartum C: ZDV and 3TC intrapartum only D: placebo	A. 33%, B. 35% C. 32% D. 33%
NVAZ Taha et al, 2004[161]	Anemic, pre-term, admission to the neonatal intensive care unit, HIV status not known	9,469 women screened, 894 randomized	5 excluded, 286 lost to follow-up A. 389 B. 408	Median age 25, median CD count not reported	A. Single oral dose of nevirapine intrapartum and single oral dose of nevirapine to infant B. Single oral dose of nevirapine intrapartum and single oral dose of nevirapine plus ZDV for 1 week to infant	A. 3.5% B. 1.1%

ELISA, enzyme-linked immunoabsorbent assay; 3TC, lamivudine; ZDV, zidovudine.

Table 10. Evidence Table: Randomized Controlled Trials of Short Courses of Combination Antiretroviral Therapy for Reduction of Mother-to-Child Transmission of HIV Infection

Study, year	Breastfeeding rate	Transmission rate	Other risk factors associated with mother-to-child transmission	Adverse events	Internal validity rating
PETRA PETRA Study Team, 2002[155]	A. 74% B. 73% C. 76% D. 74% At birth	A: 5.7% RR 0.37 (0.21-0.65) B: 8.9% RR 0.58 (0.36-0.94) C: 14.2% RR 0.93 (0.62-1.40) D: 15.3% RR 1.0 At 6 weeks postpartum	Cesarean section lowered risk of transmission OR 0.60 (0.41-0.87) Higher maternal CD4 count lowered risk of transmission OR 0.89 (0.83-0.95) per 100 CD4 cells increment Breastfeeding at 18 months associated with higher risk of transmission OR 2.18 (1.50-3.17)	No significant difference in rates of serious adverse clinical or laboratory events in mothers or infants or in congenital anomalies between treatment groups	GOOD
NVAZ Taha et al, 2004[161]	A. 99.2% B. 100% At 1 week	A. 6.5% B. 6.9% At 6-8 weeks	Maternal viral load increased rate per log 10 increase OR 2.66 (1.95-3.63)	No significant difference in rates of serious adverse clinical or laboratory events in mothers or infants between treatment groups	GOOD Open label

ELISA, enzyme-linked immunoabsorbent assay; 3TC, lamivudine; ZDV, zidovudine.

Table 11. Evidence Table: Randomized Controlled Trials and Large Observational Studies Evaluating the Association between Breastfeeding and Risk of Mother-to-Child Transmission of HIV Infection

Author, year	Type of study	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)	Exclusion criteria (baby)	Screened/eligible/ enrolled
Leroy et al, 1998[28]	Meta-analysis	To estimate the rate and timing of late (after 2.5 months) postnatal transmission of HIV	Africa, Europe, US	HIV positive	HIV negative at birth	HIV status not known	8 cohort studies: 4 in Africa and 4 in Europe or US 902 children from Africa, 2,804 children from US and Europe
Dunn et al, 1992[24]	Meta-analysis	To determine the risk of mother-to-child transmission of HIV through breast milk	Europe, US, Australia, Africa	HIV positive	Mom in study	HIV status not known	6 cohort studies, 5 in US, Europe, and Australia, 1 in Africa 296 children included
John et al, 2001[27]	Meta-analysis	To determine the frequency and timing of breast milk transmission of HIV	US, Europe, Brazil, Africa	HIV positive	Mom in study	HIV status not known	8 cohort studies, 3 from Africa, 2 from Europe, 1 US, 1 from Brazil 2,375 mother-infant pairs
BHIT Study Group, 2004[26]	Meta-analysis	To determine the contribution of late postnatal transmission through breastfeeding to the overall risk of mother-to-child transmission of HIV	Africa	Trials with completed enrollment, populations with high rates of breastfeeding, trials with assessment of children's feeding modality and HIV status by 3 months of age	Mom in study	HIV status not known	10 trials identified/9 agreed to participate All studies in Africa 5,327 mother-infant pairs data obtained/4,085 infant data analyzed

Table 11. Evidence Table: Randomized Controlled Trials and Large Observational Studies Evaluating the Association between Breastfeeding and Risk of Mother-to-Child Transmission of HIV Infection

Author, year	Treatment	Observed duration of breastfeeding	Transmission rate of HIV	Internal validity rating
Leroy et al, 1998[28]	Antiretroviral therapy treatment information not reported	Median duration 15.5 months (range 3-36 months)	Transmission rate from breastfeeding: Non-breastfed: 0% Breastfed: 5% 3.2 HIV-positive children per 100 child years of breastfeeding follow-up; 9.2% cumulative probability of late (after 2.5 months) mother-to-child transmission at 36 months for breastfed group	GOOD
Dunn et al, 1992[24]	Antiretroviral therapy treatment information not reported	Not reported	Non-breastfed: 16.8% Breastfed: 26.8% Additional risk from breastfeeding 14%	GOOD
John et al, 2001[27]	Antiretroviral therapy treatment information not reported	European studies: median duration 4 weeks African studies: median duration 5.5 months	16% increased rate of mother-to-child transmission with breastfeeding. 47% attributable risk for breastfeeding	GOOD
BHIT Study Group, 2004[26]	Antiretroviral therapy treatment information not reported	Median duration 10.0 months (range: 2.7-17.1 months)	24% overall mother-to-child transmission rate. 42% of positive children had late postnatal transmission through breastfeeding. Overall risk of late (after 4 weeks) postnatal transmission through breastfeeding 8.9 transmissions/100 child years of breastfeeding. Cumulative probability of late postnatal transmission through breast milk at 18 months was 9.3%	GOOD

Table 11. Evidence Table: Randomized Controlled Trials and Large Observational Studies Evaluating the Association between Breastfeeding and Risk of Mother-to-Child Transmission of HIV Infection

Author, year	Type of study	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)	Exclusion criteria (baby)	Screened/eligible/ enrolled
Nduati et al, 2000[164]	RCT	To determine the frequency of breast milk transmission of HIV	Nov. 1,1992-July 1998 Nairobi, Kenya	HIV positive, agree to randomization, have access to municipal water	Mom in study	HIV status not known	2,315/425/333
Coutsoudis et al, 1999[165]	Prospective cohort	To determine the risk of breastfeeding on mother-to-child transmission of HIV	July 1995-April 1998, Africa	HIV positive, 28-32 weeks gestation at enrollment	HIV status known, singleton	HIV status not known	661/549
Italian Register for HIV Infection in Children 2002[48]	Prospective cohort	To determine the risk factors for mother-to-child transmission of HIV	1985-1995 cohort and 1996-1999 cohort, Italy	HIV positive	Mom in study	HIV status not known	3,770 infants

Table 11. Evidence Table: Randomized Controlled Trials and Large Observational Studies Evaluating the Association between Breastfeeding and Risk of Mother-to-Child Transmission of HIV Infection

Author, year	Treatment	Observed duration of breastfeeding	Transmission rate of HIV	Internal validity rating
Nduati et al, 2000[164]	Randomized to breastfeeding or formula, no antiretroviral therapy	Median duration 17 months (range <1 week to >24 months)	36.7% cumulative incidence of HIV transmission with breastfeeding at 24 months vs. 20.5% for formula feeding (p=0.001) Estimated rate of breastfeeding transmission was 16.2%, breastfeeding accounted for 44% of HIV infection	GOOD
Coutsoudis et al, 1999[165]	No antiretroviral therapy	Median duration 6 months	Never breastfed: 18.8% Exclusively breastfed: 14.6% Mixed feeding: 24.1% At 3 months	GOOD
Italian Register for HIV Infection in Children 2002[48]	Any antiretroviral therapy or none	Not reported	Breastfed infants between 1996 and 1999: OR 10.20 (2.73-38.11)	GOOD

Table 12. Evidence Table: Meta-Analysis and Randomized Controlled Trial of Effects of Elective Cesarean Section on Risk of Mother-to-Child Transmission of HIV Infection

Author, year	Type of study	Aims	Study duration	Eligibility criteria (mother)	Eligibility criteria (baby)	Exclusion criteria (mother)	Exclusion criteria (baby)
European Collaborative Study, 2005[149]	Prospective cohort	To evaluate risk factors for mother-to-child transmission during the HAART era	1985-May 2004	European centers, HIV positive	Mother enrolled	Not specified	HIV status unknown
European Mode of Delivery Collaboration, 1999[171]	RCT	To assess the relative risks and benefits of elective cesarean section vs. vaginal delivery on mother-to-child transmission of HIV	1993-March 1998	European centers, HIV positive	HIV status known	Obstetric indication for cesarean section, contraindication to elective cesarean section	HIV status unknown
International Perinatal HIV Group, 1999[170]	Meta-analysis of pooled patient data	To evaluate the association between mode of delivery and risk of mother-to-child transmission of HIV	Prior to 1997	5 European and 10 US prospective cohort studies, English, agreed to participate	Eldest live birth in study period	Multiple gestation, breastfeeding, mode of delivery not known	HIV status unknown

AOR, adjusted odds ratio; HAART, highly active antiretroviral therapy; RCT, randomized controlled trial; ZDV, zidovudine.

Table 12. Evidence Table: Meta-Analysis and Randomized Controlled Trial of Effects of Elective Cesarean Section on Risk of Mother-to-Child Transmission of HIV Infection

Author, year	Eligible/enrolled	Withdrawals or lost to follow-up/Number analyzed	Antiretroviral treatment	Rate of mother-to-child transmission of HIV	Internal validity rating
European Collaborative Study, 2005[149]	Not reported/4,525	Not reported/4,525	HAART, one or two drug therapy, or no treatment	6.5% in women delivering vaginally, 2.5% in women delivering by emergency cesarean section, and 1.65% by elective cesarean section (p<0.001)	GOOD
European Mode of Delivery Collaboration, 1999[171]	436/370	55/315	Any antiretroviral therapy or no treatment	10.5% in women randomized to vaginal delivery vs. 1.8% in those randomized to elective cesarean section (p=0.009) OR 0.2 (0.1-0.6)	GOOD
International Perinatal HIV Group, 1999[170]	15,471/8,533	Not reported	ZDV monotherapy or no treatment	Elective cesarean section vs. any other mode of delivery AOR 0.43 (0.33-0.56) vs. nonelective cesarean section AOR 0.45 (0.33-0.61) vs. vaginal delivery AOR 0.42 (0.33-0.55)	GOOD

AOR, adjusted odds ratio; HAART, highly active antiretroviral therapy; RCT, randomized controlled trial; ZDV, zidovudine.

Table 13. Large Observational Studies Evaluating Adverse Effects from In Utero Exposure to Combination Antiretrovirals

Study, year	Type of study	Setting	Treatment	Congenital anomalies or adverse events	Premature delivery	Low birth weight
Tuomala et al, 2002[203]	Combination analysis of 5 prospective cohort studies	US	A. 1,590 ZDV monotherapy B. 396 combination therapy without protease inhibitor C. 137 combination therapy with protease inhibitor D. 1,143 no treatment	No significant difference between any treatment group and controls	A vs. D: AOR 0.70 (95% CI, 0.49-1.01) B vs. D: AOR 0.95 (95% CI, 0.51-1.69) C vs. D: AOR 1.50 (95% CI, 0.72-3.01) A. vs. B or C: AOR 1.08 (95% CI, 0.71-1.62)	A vs. D: AOR 0.89 (95% CI, 0.62-1.29) B vs. D: AOR 0.45 (95% CI, 0.20-0.92) C vs. D: AOR 1.36 (95% CI, 0.27-5.14) A vs. B or C: AOR 1.03 (95% CI, 0.64-1.63)
European Collaborative Study and the Swiss Mother+Child HIV Cohort Study, 2000[223]	Prospective cohort	Europe	323 mother-child pairs exposed to 2 or more drug antiretroviral therapy	Not reported	Combination treatment without protease inhibitor: AOR 1.82 (95% CI, 1.13-2.92) vs. no treatment Combination treatment with protease inhibitor: AOR 2.60 (95% CI 1.43-4.75) vs. no treatment	Not reported
European Collaborative Study, 2003[204]	Prospective cohort	Europe	A. 235 infants exposed to combination therapy without protease inhibitor B. 196 infants exposed to combination therapy with protease inhibitor C. 1983 infants with no treatment	No significant association between antiretroviral treatment and mitochondrial dysfunction	A vs. C: AOR 2.66 (95% CI 1.52-4.67) B vs. C: AOR 4.14 (95% CI 2.36 -7.23)	No association with antiretroviral therapy

Table 13. Large Observational Studies Evaluating Adverse Effects from In Utero Exposure to Combination Antiretrovirals

Study, year	Type of study	Setting	Treatment	Congenital anomalies or adverse events	Premature delivery	Low birth weight
European Collaborative Study, 2001[39]	Prospective cohort study	Europe	3,076 infants exposed to any antiretroviral therapy or no therapy	No significant differences in congenital anomalies compared to unexposed; severe neurological abnormalities seen in 2 exposed and 9 unexposed HIV negative infants, no reports of mitochondrial abnormalities	Not reported	Not reported

AOR, adjusted odds ratio; ZDV, zidovudine

Table 14. Evidence Table: Large Observational Studies and Meta-Analyses Evaluating Association between In Utero Exposure to Antiretroviral Therapy and Infant Adverse Effects

Author, year	Type of study	Aims	Study duration and location	Eligibility criteria (mother)	Eligibility criteria (baby)
Tuomala et al, 2002[203]	Meta-analysis	Assess adverse effects of antiretroviral therapy on pregnancy outcomes	Jan. 1, 1990-March 1, 1998 US	HIV positive Membership in one of 7 prospective cohort studies: PACTG 076, PACTG 185, PACTS, WITS, studies at University of Miami, USC, and UCLA	Mom in study
European Collaborative Study and the Swiss Mother+Child HIV Cohort Study, 2000[223]	Prospective cohort study	Assess association between type of antiretroviral therapy in pregnancy and rate of premature birth	1986-April 2000 Europe	HIV positive	Mom in study
European Collaborative Study 2003[204]	Prospective cohort study	Assess effects of antiretroviral exposure on perinatal outcomes	1986-Dec. 2001 Europe	HIV positive	HIV negative, mom in study
European Collaborative Study, 2001[39]	Prospective cohort study	To describe changes in characteristics and management of HIV-positive women in Europe over 15 years	1986-June 2000 Europe	HIV positive	Mom in study

AOR, adjusted odds ratio; 3TC, lamivudine; ZDV, zidovudine.

Table 14. Evidence Table: Large Observational Studies and Meta-Analyses Evaluating Association between In Utero Exposure to Antiretroviral Therapy and Infant Adverse Effects

Author, year	Screened/eligible/enrolled	Treatment	Clinical outcomes for infant
Tuomala et al, 2002[203]	2,123 mother-infant pairs	A. 1,590 ZDV monotherapy B. 396 combination therapy without protease inhibitor C. 137 combination therapy with protease inhibitor D. 1,143 no treatment	No significant differences in congenital anomalies or serious clinical or laboratory abnormalities between infants with no exposure and infants with exposure to any group of antiretroviral medications
European Collaborative Study and the Swiss Mother+Child HIV Cohort Study, 2000[223]	323 mother-infant pairs	132 ZDV+3TC 191 other 2 drug antiretroviral regimens	Not reported
European Collaborative Study 2003[204]	2,845 infants	A. 235 infants exposed to combination therapy without protease inhibitor B. 196 infants exposed to combination therapy with protease inhibitor C. 1,983 infants with no treatment	No significant association between antiretroviral treatment and mitochondrial dysfunction
European Collaborative Study, 2001[39]	2,876 women with 3,076 babies	Any antiretroviral treatment regimen or no treatment	No significant differences in congenital anomalies on infants exposed to antiretroviral therapy compared to unexposed; severe neurological abnormalities seen in 2 exposed and 9 unexposed HIV-negative infants, no reports of mitochondrial abnormalities

AOR, adjusted odds ratio; 3TC, lamivudine; ZDV, zidovudine.

Table 14. Evidence Table: Large Observational Studies and Meta-Analyses Evaluating Association between In Utero Exposure to Antiretroviral Therapy and Infant Adverse Effects

Author, year	Premature delivery	Low birth weight	Internal validity rating
Tuomala et al, 2002[203]	A vs. D: AOR 0.70 (0.49-1.01) B vs. D: AOR 0.95 (0.51-1.69) C vs. D: AOR 1.50 (0.72-3.01) A. vs. B or C: AOR 1.08 (0.71-1.62)	A vs. D: AOR 0.89 (0.62-1.29) B vs. D: AOR 0.45 (0.20-0.92) C vs. D: AOR 1.36 (0.27-5.14) A vs. B or C: AOR 1.03 (0.64-1.63)	GOOD
European Collaborative Study and the Swiss Mother+Child HIV Cohort Study, 2000[223]	Combination treatment without protease inhibitor vs. no treatment: AOR 1.82 (95% CI, 1.13-2.92) Combination treatment with protease inhibitor vs. no treatment: AOR 2.60 (95% CI 1.43-4.75)	Not reported	GOOD
European Collaborative Study 2003[204]	A vs. C: AOR 2.66 (95% CI 1.52-4.67) B vs. C: AOR 4.14 (95% CI 2.36 -7.23)	No association with antiretroviral therapy	GOOD
European Collaborative Study, 2001[39]	Not reported	Not reported	GOOD

AOR, adjusted odds ratio; 3TC, lamivudine; ZDV, zidovudine.

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
1	Does screening for HIV in asymptomatic pregnant women reduce mother-to-child transmission or premature death and disability?	None	Not applicable	No controlled studies or observational studies link screening directly to health outcomes.
2	Can clinical or demographic characteristics (including persons in specific settings) identify subgroups of asymptomatic pregnant women at increased risk for HIV infection compared to the general population of pregnant women?	II-2. Cohort and cross-sectional studies	FAIR	The strongest risk factors for HIV infection from multiple large observational studies are high-risk sexual behaviors and intravenous drug use. Observational studies from before 1995 found that 8%-58% of HIV-positive pregnant women reported identifiable risk factors, but often did not assess the number of unprotected sexual partners. Universal counseling and voluntary screening appears to increase the yield of HIV diagnoses compared to targeted screening. In a seven-state surveillance study, the proportion of HIV-infected women diagnosed before delivery increased from 70% to 80% after the introduction of universal counseling.
3	What are the test characteristics of HIV antibody test strategies in pregnant women?	Studies of diagnostic test accuracy	GOOD for standard and rapid tests (OraQuick®) POOR for other screening methods	Standard testing is associated with a sensitivity and specificity of >99%. One study of Oraquick® rapid testing in women with unknown HIV status presenting to labor and delivery units found similar accuracy, but data from clinical settings are limited for other FDA-approved rapid tests. Other screening technologies (home sampling, oral and urine specimens) have not been well studied in pregnant women.

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
4	What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to pregnant women?	Studies of diagnostic test accuracy II-2. Cohort and cross-sectional studies for harms of screening and acceptability	GOOD for false-positive rates and false-negative rates FAIR to GOOD for harms from screening and acceptability of testing	False-positive results appear rare with standard testing, even in low-prevalence settings. Indeterminate test results may be slightly more common in pregnant or parous women. False-positive tests from rapid tests could occur if results are given prior to confirmatory testing. In a labor and delivery setting, 4 out of 4,849 pregnant women briefly received unnecessary interventions after initial false-positive rapid test results in one study. False-negative results could occur during the window period before seroconversion and provide false reassurance. True-negative tests could also provide false reassurance in patients practicing high-risk behaviors. True-positive tests are associated with social consequences, anxiety, and labeling, but these harms are difficult to measure. A recent good-quality cohort study found that the rate of violence during pregnancy was similar between HIV-infected women and matched controls. Risks of partner dissolution, and suicide risk have not been well studied in pregnant women. A good-quality systematic review found that acceptance rates for voluntary HIV antibody testing among pregnant women ranged widely from 23% to 100%. Testing rates appeared to be higher in states and provinces that used an 'opt-out' (pregnant women are informed that an HIV test is being conducted as a standard part of prenatal care and that they may refuse it) compared to an 'opt-in' (pregnant women are required to consent specifically to an HIV test) policy (71% to 98% vs. 25% to 83%, respectively). Rapid tests in labor and delivery units were associated with an acceptance rate of 84% in a good-quality prospective study. Over 90% of tested pregnant women returned for results in one large U.S. study.

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
5	How many HIV-infected pregnant women who meet criteria for interventions receive them?	II-2. Cohort and cross-sectional studies	FAIR for CD4 count at time of diagnosis GOOD for acceptability of interventions	All HIV-infected pregnant women are eligible for antiretroviral prophylaxis to reduce the risk of mother-to-child transmission. Eligibility for antiretroviral treatment (to improve maternal outcomes) is determined by CD4 count and viral loads. One large U.S. cohort study found that 13% (70/546) of HIV-infected pregnant women had a CD4 count <200 cells/mm^3, which could affect the choice of long-term maternal antiretroviral therapy. Antiretroviral prophylaxis and other strategies for reduction of mother-to-child transmission appear to be widely acceptable to pregnant women, with more than 90% of HIV-positive women receiving antiretrovirals during pregnancy, and an increasing proportion (58%-80%) receiving combination regimens. 37%-50% of women with known HIV infection underwent elective cesarean section since 1998 in the United States.
6	What are the harms associated with the work-up for HIV infection in pregnant women?	None	Not applicable	No evidence

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7a	1) How effective is antiretroviral prophylaxis (to prevent mother-to-child transmission) or treatment (to improve maternal outcomes) in reducing transmission rates or improving clinical outcomes (mortality, functional status, quality of life, symptoms, or opportunistic infections) in pregnant women with HIV infection?	I, II-2. Randomized controlled trial, large cohort studies	GOOD	A good-quality clinical trial (PACTG 076) found that 3-part zidovudine prophylaxis decreased mother-to-child transmission from 25% to 8%. Large observational studies found that antiretroviral regimens with more drugs were superior to regimens with fewer drugs for reducing mother-to-child transmission. A large, good-quality observational study found that HAART significantly reduced mother-to-child transmission compared to no antiretroviral therapy (adjusted odds ratio 0.13, 95% confidence interval 0.06 to 0.27). A recent good-quality randomized trial of slightly shortened zidovudine plus single doses of nevirapine found rates of transmission (1.9%) comparable to those of full-course combination antiretroviral regimens. Other short courses of antiretroviral prophyhlaxis were less effective than full courses, but could be useful in HIV-infected women diagnosed late in pregnancy. There were insufficient data to estimate long-term effects of antiretrovirals started during pregnancy and either continued or interrupted.
7a	2) How effective is avoidance of breastfeeding in reducing mother-to-child transmission rates in pregnant women with HIV infection?	I, II-2. Randomized controlled trial, cohort studies	GOOD	In two meta-analyses, breastfeeding was associated with an increase in overall absolute rate of vertical transmission of 14% and 16%. One African randomized controlled trial found that breastfeeding reduced the probability of vertical transmission at 24 months from 37% to 20%. One European observational study in women who received antiretroviral treatment found that breastfeeding significantly increased rates of mother-to-child transmission (OR 10.20, 95% CI, 2.73, 38.11).

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7a	3) How effective is elective cesarean section or other labor management practices in reducing mother-to-child transmission rates in pregnant women with HIV infection?	I, II-2. Randomized controlled trial and meta-analysis of cohort studies	GOOD	One good-quality European cohort study evaluated the effectiveness of elective cesarean section in the HAART era. It found an odds ratio of 0.33 (95% CI 0.11 to 0.94) for mother-to-child transmission with elective cesarean section compared to vaginal delivery when adjusted for other factors including antiretroviral therapy and maternal viral load. Other studies were conducted prior to the widespread use of HAART. One good-quality randomized controlled trial found that elective cesarean section reduced the rate of mother-to-child transmission of HIV from 10.5% to 1.8%. A meta-analysis of 15 cohort studies found that elective cesarean section reduced the risk of vertical transmission compared to other modes of delivery (OR 0.43, 95% CI, 0.33, 0.56). Elective cesarean section appeared effective in women with viral loads <1000 copies/ml, but transmission rates were very low with antiretroviral treatment alone (about 1%). The effectiveness of other labor management practices has not been well studied.
7a	4) How effective is counseling on risky behaviors in reducing mother-to-child transmission rates in pregnant women with HIV infection?	None	Not applicable	No evidence

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7a	5) How effective are immunizations, routine monitoring and follow-up, or prophylaxis for opportunistic infections in reducing mother-to-child transmission rates or improving clinical outcomes in pregnant women with HIV infection?	None	Not applicable	No evidence specifically in pregnant women
7b	Does immediate antiretroviral treatment in HIV-infected pregnant women result in improvements in clinical outcomes compared to delayed treatment until symptomatic?	None	Not applicable	We identified no studies estimating the effects of delayed or discontinued versus continuous HAART in HIV-infected women identified during pregnancy. We also identified no studies examining the effects of withholding first trimester antiretrovirals on mother-to-child transmission rates or other clinical outcomes.
7c	How well do interventions reduce the rate of viremia, improve CD4 counts, or reduce risky behaviors? How does identification of HIV infection in pregnant women affect future reproductive choices?	I, II-2. Randomized controlled trials, cohort studies	GOOD	HAART is highly effective in reducing viral loads and increasing CD4 counts in pregnant women. There is insufficient evidence to determine the effects of HIV diagnosis during pregnancy on risky behaviors associated with vertical or horizontal transmission. Tubal ligation rates among HIV-infected pregnant women were 24% to 27% in three studies, and may be higher than in HIV-negative controls. Abortion rates do not appear higher among HIV-infected compared to uninfected women. There were insufficient data to determine the effects of HIV diagnosis during pregnancy on other future reproductive choices (pregnancy rates, contraceptive use).

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
8	What are the harms associated with antiretroviral drugs (including adverse effects from in utero exposure) and elective cesarean section?	I, II-2. Randomized controlled trials, cohort studies	GOOD	Antiretroviral exposure during pregnancy is associated with significant non-obstetric adverse events for the mother, but these are usually short-term and resolve after stopping or changing the offending drug or drug combination. Serious or fatal maternal events appear rare on zidovudine alone and currently recommended combination regimens. One recent randomized controlled trial of combination antiretrovirals was discontinued early (N=38) because of a high rate of treatment-limiting hepatitis or cutaneous toxicity with continuous nevirapine (29%) compared to nelfinavir (5%) in combination with zidovudine. Another trial found lower 6-month virologic response rates (49% versus 68%) after maternal exposure to a single dose of peripartum nevirapine and continuous nevirapine-based treatment after delivery. We identified no studies evaluating the effects of limited exposure to combination antiretrovirals during pregnancy on subsequent long-term clinical progression or response to later antiretroviral therapy. Cohort studies have found a higher rate of postpartum complications in HIV-infected women who underwent cesarean section compared to HIV-infected women who delivered vaginally. The largest study found a relative risk of 2.62 (95% CI, 1.61, 4.20) compared to vaginal delivery. No increase in any specific fetal abnormality has been identified with currently recommended antiretroviral regimens, but there are relatively little data on the in utero safety of antiretroviral regimens. Evidence regarding the association between combination antiretrovirals and premature delivery was mixed. Cohort studies of infants exposed to zidovudine in utero have found no evidence of long-term complications up to 6 years after exposure.

Table 15. Summary of Findings of Systematic Evidence Review of HIV Screening for Pregnant Women

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
9	Have improvements in intermediate outcomes (CD4 counts, viremia, or risky behaviors) in HIV-infected pregnant women been shown to improve clinical outcomes or reduce mother-to-child transmission?	II-2. Cohort and cross-sectional studies	GOOD for viral loads POOR for behavior changes	Reduced viral loads have been consistently associated with reduced rates of mother-to-child transmission of HIV in clinical trials and observational studies. Several behaviors (unprotected intercourse, smoking, hard drug use) are associated with an increased risk of vertical transmission, but we identified no studies evaluating the association between changes in these behaviors and subsequent mother-to-child transmission rates.

HAART, highly active retroviral therapy.

Table 16. Outcomes Table of Screening for HIV Infection in 10,000 Asymptomatic Pregnant Women

Variable	0.15% prevalence	0.30% prevalence	High risk	Source
Base-case assumptions				
Prevalence of HIV infection	0.15%	0.30%	5%	CDC, 2002[10] Lindegren et al, 1999[5] Fehrs et al, 1988[71] Barbacci et al, 1990[72]
Accuracy of standard testing	99%+	99%+	99%+	CDC, 1990[89] CDC, 1998[67]
Proportion receiving test results	91%	91%	91%	Joo, 2000[132]
Proportion receiving antiretroviral therapy	60%-90%	60-90%	60-90%	CDC, 2004[134] CDC, 2002[135] Wade et al, 2004[136] Fiscus et al, 2002[137] Cooper et al, 2002[37]
Proportion receiving elective cesarean section	37-50%	37-50%	37-50%	Fiscus et al, 2002[137] Dominguez et al, 2003[138] CDC, 2004[134]
Rate of mother-to-child transmission in absence of interventions	14-25%	14-25%	14-25%	Working Group on Mother-to-Child Transmission of HIV, 1995[145]
Relative risk for mother-to-child-transmission with HAART compared to no antiretrovirals	0.13 (95% CI, 0.06 to 0.27)	0.13 (95% CI, 0.06 to 0.27)	0.13 (95% CI, 0.06 to 0.27)	European Collaborative Study, 2005[149]
Rate of postpartum complications in HIV-infected women delivering vaginally	10.3% (95% CI, 8.39 to 12.6)	10.3% (95% CI, 8.39 to 12.6)	10.3% (95% CI, 8.39 to 12.6)	Read et al, 2001[199]
Relative risk of postpartum complications from elective cesarean section	2.62 (95% CI, 1.61 to 4.20)	2.62 (95% CI, 1.61 to 4.20)	2.62 (95% CI, 1.61 to 4.20)	Read, 2001[199]

(results on next page)

Table 16. Outcomes Table of Screening for HIV Infection in 10,000 Asymptomatic Pregnant Women

Variable	0.15% prevalence	0.30% prevalence	High risk
Results			
Number identified as positive	15.0000	30.0000	500.0000
Number receiving test results	13.6000	27.3000	455.0000
Number of cases of mother-to-child transmission expected without interventions among women receiving test results	1.9-3.4	3.8-6.8	64-114
Number receiving combination antiretroviral therapy	8.2-12.3	16.4-24.6	273-410
Number receiving elective cesarean section	5.0-6.8	10.1-13.6	168-228
Number of cases of mother-to-child transmission prevented with HAART	1.0 (95% CI, 0.8 to 1.1) - 2.7 (95% CI, 2.2 to 2.8)	2.0 (95% CI, 1.6 to 2.1) - 5.3 (95% CI, 4.4 to 5.7)	33 (95% CI, 27 to 36) - 88 (95% CI, 73 to 95)
Number needed to screen to prevent 1 case of mother-to-child transmission of HIV with HAART	3780 (95% CI, 3500 to 4549) - 10120 (95% CI, 9380 to 12170)	1890 (95% CI, 1750 to 2270) - 5060 (95% CI, 4690 to 6090)	113 (95% CI, 105 to 136) - 304 (95% CI, 282 to 365)
Number needed to treat with interventions to prevent 1 case of mother-to-child transmission of HIV with HAART	4.6 (95% CI, 4.3 to 5.5) - 8.2 (95% CI, 7.6 to 9.9)	4.6 (95% CI, 4.3 to 5.5) - 8.2 (95% CI, 7.6 to 9.9)	4.6 (95% CI, 4.3 to 5.5) - 8.2 (95% CI, 7.6 to 9.9)
Number of postpartum complications caused by elective cesarean section	0.8 (95% CI, 0.3 to 1.7) - 1.1 (95% CI, 0.4 to 2.3)	1.7 (95% CI, 0.6 to 3.5) -2.3 (95% CI, 0.8 to 4.7)	28 (95% CI, 11 to 58) - 38 (95% CI, 14 to 78)
Number needed to screen to cause 1 postpartum complication from elective cesarean section	8810 (95% CI, 4280 to 23420) -11910 (95% CI, 5780 to 31640)	4400 (95% CI, 2140 to 11700) - 5950 (95% CI, 2880 to 15820)	260 (95% CI, 130 to 700) -357 (95% CI, 170 to 940)
Number needed to treat to cause 1 postpartum complication from elective cesarean section	6.0 (95% CI, 2.9 to 15.9)	6.0 (95% CI, 2.9 to 15.9)	6.0 (95% CI, 2.9 to 15.9)

HAART, highly active antiretroviral therapy.

Search Strategies

Immunization

Database: MEDLINE® <1996-present>

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1 exp hiv infections/ or exp hiv/
2 exp Viral Hepatitis Vaccines/
3 exp Influenza Vaccine/
4 exp Bacterial Vaccines/
5 2 or 3 or 4
6 1 and 5
7 exp IMMUNIZATION/
8 exp Immunization Programs/
9 7 or 8
10 exp HEPATITIS/
11 exp INFLUENZA/
12 exp PNEUMONIA/
13 10 or 11 or 12
14 1 and 9 and 13
15 6 or 14
16 exp Evaluation Studies/
17 exp Epidemiologic Studies/
18 Comparative Study/
19 16 or 17 or 18
20 15 and 19
21 limit 15 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline)
22 20 or 21
23 limit 22 to (human and english language)
24 from 23 keep 1-206

Prophylaxis

Database: MEDLINE® <1996-present>

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1 exp AIDS-Related Opportunistic Infections/pc [Prevention & Control]
2 prophyla$.mp.
3 exp HIV Infections/co [Complications]
4 exp AIDS-Related Opportunistic Infections/
5 2 and (3 or 4)

6 1 or 5
7 limit 6 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
8 from 7 keep 1-396

Counseling

Database: MEDLINE® <1996-present>
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1 exp HIV Infections/ or exp HIV/
2 exp COUNSELING/
3 1 and 2
4 exp impulsive behavior/ or risk reduction behavior/ or risk-taking/
5 1 and 4
6 3 or 5
7 exp Evaluation Studies/
8 Comparative Study/
9 exp Epidemiologic Studies/
10 7 or 8 or 9
11 6 and 10
12 limit 6 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline)
13 11 or 12
14 limit 13 to (human and english language)
15 from 14 keep 1-1272

Risk Factors

Database: MEDLINE® <1996-present>
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1 exp RISK/
2 exp HIV Infections/mo, ep, eh, et, tm, pc [Mortality, Epidemiology, Ethnology, Etiology, Transmission, Prevention & Control]
3 1 and 2
4 limit 3 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
5 exp HIV/
6 1 and 5
7 limit 6 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
8 4 or 7
9 exp Evaluation Studies/
10 Comparative Study/

11 exp Epidemiologic Studies/
12 9 or 10 or 11
13 (3 or 6) and 12
14 limit 13 to (human and english language)
15 from 8 keep 1-573

Screening

Database: MEDLINE® <1996-present>
---
1 exp AIDS Serodiagnosis/
2 exp HIV SERONEGATIVITY/ or exp HIV ANTIGENS/ or exp HIV/ or exp HIV SEROPREVALENCE/ or exp HIV SEROPOSITIVITY/ or exp HIV ANTIBODIES/
3 exp Mass Screening/
4 2 and 3
5 1 or 4
6 exp "Sensitivity and Specificity"/
7 5 and 6
8 ae.fs.
9 exp stress, psychological/
10 Life Change Events/
11 exp prejudice/ or prejudic$.mp.
12 8 or 9 or 10 or 11
13 5 and 12
14 exp diagnostic errors/
15 5 and 14
16 7 or 13 or 15
17 exp Evaluation Studies/
18 Comparative Study/
19 exp longitudinal studies/
20 17 or 18 or 19
21 16 and 20
22 limit 16 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline or review)
23 22 or 21
24 limit 23 to (human and english language)
25 limit 23 to (human and abstracts)
26 24 or 25
27 from 26 keep 1-247

Antiviral Drugs

Database: MEDLINE® <1998-present>

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1 exp HIV Infections/dt [Drug Therapy]
2 exp HIV/de [Drug Effects]
3 1 or 2
4 exp Reverse Transcriptase Inhibitors/ad, tu
5 exp HIV Protease Inhibitors/ad, tu
6 exp anti-hiv agents/ad, tu
7 4 or 5 or 6
8 3 and 7

9 limit 8 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
10 exp Reverse Transcriptase Inhibitors/ae, ct, to, po
11 exp HIV Protease Inhibitors/ae, ct, to, po
12 exp anti-hiv agents/ae, ct, to, to
13 10 or 11 or 12
14 3 and 13
15 limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16 14 and exp epidemiologic studies/
17 14 and (exp evaluation studies/ or exp comparative study/)
18 16 or 17
19 limit 18 to (human and english language)
20 15 or 19
21 limit 9 to yr=1998-2003
22 from 21 keep 1-1157

Adverse Effects

Database: MEDLINE® <1998-present>

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1 exp HIV Infections/dt [Drug Therapy]
2 exp HIV/de [Drug Effects]
3 1 or 2
4 exp Reverse Transcriptase Inhibitors/ad, tu
5 exp HIV Protease Inhibitors/ad, tu
6 exp anti-hiv agents/ad, tu
7 4 or 5 or 6
8 3 and 7

9 limit 8 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
10 exp Reverse Transcriptase Inhibitors/ae, ct, to, po
11 exp HIV Protease Inhibitors/ae, ct, to, po
12 exp anti-hiv agents/ae, ct, to, to
13 10 or 11 or 12
14 3 and 13
15 limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16 14 and exp epidemiologic studies/
17 14 and (exp evaluation studies/ or exp comparative study/)
18 16 or 17
19 limit 18 to (human and english language)
20 15 or 19
21 limit 9 to yr=1998-2003
22 from 21 keep 1-1157
23 limit 20 to yr=1998-2003

24 from 23 keep 1-732
25 from 24 keep 1-732

Workup

Database: MEDLINE® <1998-present>
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1 exp HIV/
2 viral load.mp. or Viral Load/
3 VIREMIA/
4 exp HIV Infections/
5 1 or 4
6 2 or 3
7 5 and 6
8 (exp leukocyte count/ and cd4.mp.) or exp cd4 lymphocyte count/
9 exp "pathological conditions, signs and symptoms"/ or disease progression/
10 7 and 8 and 9
11 exp "sensitivity and specificity"/
12 10 and 11
13 exp epidemiologic studies/
14 10 and 13
15 limit 10 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16 limit 14 to (human and english language)
17 15 or 16
18 from 17 keep 1-232

Maternal

Database: MEDLINE® <1996-present>

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1 exp HIV/ or exp HIV INFECTIONS/
2 exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
3 exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
4 exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]
5 1 and (2 or 3 or 4)
6 exp Disease Transmission, Vertical/
7 exp HIV Infections/tm
8 pregnancy complications/ or exp pregnancy complications, infectious/
9 exp Pregnancy/
10 6 or 7
11 8 or 9

12 10 and 11
13 5 and 12
14 limit 13 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
15 exp Evaluation Studies/
16 Comparative Study/
17 exp Epidemiologic Studies/
18 15 or 16 or 17
19 13 and 18
20 limit 19 to (human and english language)
21 14 or 20
20 from 21 keep 1-373

Cesarean

Database: MEDLINE® <1996-present>

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1. exp HIV/ or exp HIV INFECTIONS/
2. exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
3. exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
4. exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]
5. exp cesarean section/

6. 1 and (2 or 3 or 4 or 5)
7. exp Disease Transmission, Vertical/
8. exp HIV Infections/tm
9. pregnancy complications/ or exp pregnancy complications, infectious/
10. exp Pregnancy/
11. 7 or 8
12. 9 or 10
13. 11 and 12
14. 6 and 13
15. limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16. exp Evaluation Studies/
17. Comparative Study/
18. exp Epidemiologic Studies/
19. 16 or 17 or 18
20. 14 and 19
21. limit 20 to (human and english language)
22. 15 or 21

Cost of Screening

Database: MEDLINE® <1996-present>

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1 exp HIV Infections/
2 exp HIV/
3 1 or 2
4 exp "Costs and Cost Analysis"/
5 3 and 4
6 Comparative Study/
7 exp Evaluation Studies/
8 exp epidemiologic study characteristics/
9 5 and (6 or 7 or 8)
10 limit 9 to (human and english language)
11 exp Mass Screening/
12 9 and 11
13 5 and 11
14 limit 13 to (human and english language)
15 ec.fs.
16 3 and 15
17 16 and 11
18 limit 17 to (human and english language)
19 14 or 18
20 from 19 keep 1-179

Systematic Reviews

Database: PubMED

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1 hiv/de [mh] OR hiv infections/dt [mh]
2 anti hiv agents[pa] OR reverse transcriptase inhibitors[pa] OR hiv protease inhibitors [pa]
3 #1 OR #2
4 evaluation studies[mh] OR epidemiologic studies[mh] OR comparative study [mh]
5 #3 AND #4
6 tu[sh] OR ad[sh] OR ae[sh] OR to[sh] OR po[sh] OR ct[sh]
7 #5 AND #6
8 #7 AND systematic [sb]
9 #8 AND Limits: Publication Date from 1989 to 1997, English, Human

NOTE: Systematic [sb] represents the following strategy as taken from the Clinical Queries search help page within PubMed.

((systematic review$ OR systematic literature review$ OR meta-analysis.pt. OR meta-analysis.ti. OR metaanalysis.ti. OR meta-analyses.ti. OR evidence-based medicine OR (evidence-based AND (guideline.tw. OR guidelines.tw. OR recommendations)) OR (evidenced-based AND (guideline.tw. OR guidelines.tw. OR recommendation$)) OR consensus development conference.pt. OR health

planning guidelines OR guideline.pt. OR cochrane database syst rev OR acp journal club OR health technol assess OR evid rep technol assess summ OR evid based nurs OR evid based ment health OR clin evid) OR ((systematic.tw. OR systematically OR critical.tw. OR (study.tw. AND selection.tw.) OR (predetermined OR inclusion AND criteri$.tw.) OR exclusion criteri$ OR main outcome measures OR standard of care) AND (survey.tw. OR surveys.tw. OR overview$ OR review.tw. OR reviews OR search$ OR handsearch OR analysis.tw. OR critique.tw. OR appraisal OR (reduction AND risk AND (death OR recurrence))) AND (literature.tw. OR articles OR publications.tw. OR publication.tw. OR bibliography.tw. OR bibliographies OR published OR unpublished OR citation OR citations OR database OR internet.tw. OR textbooks.tw. OR references OR trials OR meta-analysis.mh. OR (clinical.tw. AND studies) OR treatment outcome)) NOT(case report.ti. OR case report.mh. OR editorial.ti. OR editorial.pt. OR letter.pt. OR newspaper article.pt.))

Inclusion / Exclusion Criteria By Key Question

For key question 1, we included randomized trials and observational studies that compared clinical outcomes in patients screened and not screened for HIV infection.

For key question 2, we included recent large U.S. observational studies reporting the prevalence of HIV in patients with different risk factors, and observational studies reporting results of risk factor assessment for targeted screening.

For key questions 3 and 4, we included studies that evaluated the diagnostic accuracy of screening tests for HIV infection and performed an appropriate reference standard on all tests. We focused on Food and Drug Administration-approved rapid HIV screening tests and included published and unpublished studies on the diagnostic accuracy of these.

For key question 5, we included recent large U.S. observational studies reporting CD4 counts or viral loads at the time of diagnosis or presentation, the proportion of patients diagnosed with HIV infection within one year of being diagnosed with AIDS, and clinical trials and observational studies reporting long-term effects of late diagnosis. We also included clinical trials and observational studies reporting uptake of voluntary HIV testing, rates of return for post-test counseling, and proportion of patients qualifying for interventions who were receiving them.

For key question 6, we included studies reporting harmful effects from performing CD4 count and HIV viral load testing in patients found to be positive, such as labeling, anxiety, and effects on close partnerships.

For key questions 7a, 7b, and 7c, we included controlled trials of interventions (highly active antiretroviral therapy [HAART], counseling, routine monitoring and follow-up, pap smears, immunizations, chemoprophylaxis for opportunistic infections) that evaluated relevant intermediate (viral load, CD4 counts, behavior changes) or clinical outcomes (clinical progression, mortality, quality of life, functional status, spread of disease) in treatment-naïve populations. We included only fully published head-to-head trials of HAART. We also included large observational studies on the effects of HAART on mortality, the effectiveness of immediate versus deferred HAART, and for interventions (such as counseling) for which there was insufficient data from clinical trials.

For key question 8, we included controlled trials and observational studies that reported adverse events from HAART in treatment-naïve populations. We focused on studies reporting risks of long-term cardiovascular harms from HAART.

For key question 9, we included randomized trials and large observational studies evaluating the relationship between changes in intermediate outcomes (viral load, CD4 count, and behavior change) and clinical outcomes (AIDS, death, spread of disease, and health-related quality of life) in patients receiving HAART and counseling.

Diagnostic Accuracy Studies

Criteria

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions

- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

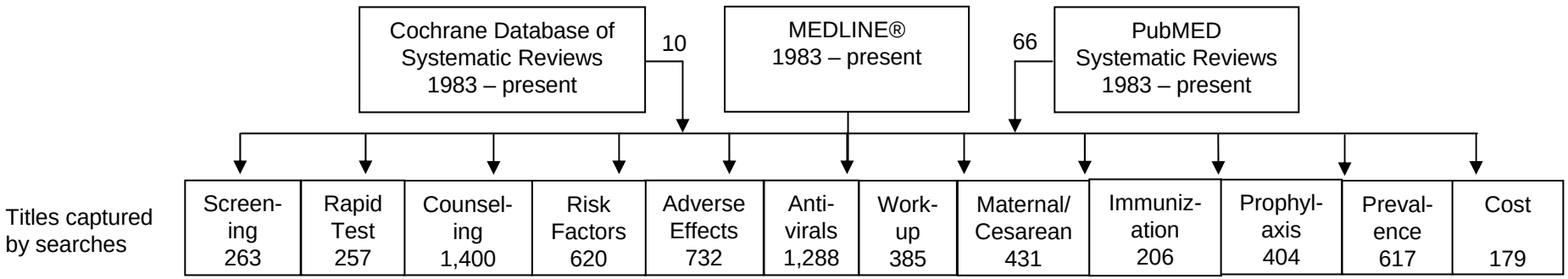
Definition of ratings based on criteria above

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Appendix D. Search and Selection Of Literature



Duplicates & non-English deleted – 865 → **5,993 abstracts reviewed for inclusion/exclusion**

Papers added from other sources + 781 → **2,647 papers reviewed for inclusion/exclusion**

Papers included in report

Key Question	RCT	Systematic review	Meta-analysis	Cohort study
7a Interventions				
Antiretroviral therapy	34			
Counseling	7	2		
Immunization	2			
Opportunistic infection PCP	6	2		
Opportunistic infection MAC	6			
Opportunistic infection TB	2			
Opportunistic infection CMV	3			
7b Delayed treatment				10
8 Cardiovascular risk			2	8

RCT, randomized control trial; PCP, pneumocystis carinii pneumonia; MAC, mycobacterium avium complex; TB, mycobacterium tuberculosis ; CMV, cytomegalovirus.

Appendix E. Statistical Methods Used For Outcomes Table (Table 16)

Calculation of numbers needed to screen (NNS) and numbers needed to treat (NNT)

Calculations of NNS and NNT were based on estimates from different sources in the literature (Table 16). The indicated range of estimates and variation associated with estimates were incorporated in the calculations and reflected by the ranges in the calculated NNS and NNT. Variation associated with the estimates was estimated using Monte Carlo simulations. The distributions of the estimates used in the simulations were either the underlying distribution on which the calculation of 95% confidence interval (CI) was based, or one that best approximated the point estimate and CI. For example, if the estimate was a rate or proportion, the logit of the rate or proportion was sampled assuming an approximately normal distribution, and then transformed back to its original scale. For relative risk, we assumed that the log of relative risk was approximately normally distributed. The point estimates and 95% CI of NNS and NNT were based on 1,000,000 simulations.

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